KINETICS AND STEREOCHEMISTRY OF THE HYDROLYSIS OF ESTERS OF NITRIC, SULFURIC AND p-TOLUENESULFONIC ACIDS

Thesis by

Pierre J. Leroux

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ABSTRACT

Unlike the hydrolysis of carboxylic esters or that of alkyl halides, the hydrolysis of esters derived from oxygenated acids of nitrogen, phosphorus, sulfur and the halogens has not been subjected to a systematic investigation.

This work represents an attempt to clarify the mechanism operating in the hydrolysis of alkyl sulfonates, sulfates and nitrates.

2-Butanol and 2,3-butanediol were chosen as the alcoholic constituents because they afforded easily obtainable optical isomers and also because of their intermediate position as secondary alkyl derivatives.

The study of the kinetics and stereochemistry of their hydrolysis has revealed that sec-butyl p-toluenesulfonate and sec-butyl nitrate resemble the secondary halides while sec-butyl hydrogen sulfate behaves much like the corresponding carboxylic esters.

The study of 3-hydroxy-sec-butyl hydrogen sulfate has afforded a reasonable explanation of the complex behavior of the cyclic sulfate of 2,3-butanediol upon hydrolysis.

An improvement in the synthesis of D(+)-sec-butyl bromide has lead to the preparation of L(-)-sec-butyl nitrate with a relatively high degree of optical activity.

Finally a new preparation of L(-)-2-butanol from D(-)-2,3-butanediol is described.

TABLE OF CONTENTS

TABLE OF CONTENTS (Cont.)

I. THE MECHANISM OF HYDROLYSIS OF *sec*-BUTYL *p*-TOLUENESULFONATE: PART 2: FURTHER INVESTIGATIONS, USING THE OPTICALLY ACTIVE COMPOUND.*

* Part 1 of this work was presented as a partial requirement for the degree of Master of Science, California Institute of Technology, 1949.

FURTHER INVESTIGATIONS ON THE MECHANISM OF HYDROLYSIS OF *sec*-BUTYL *p*-TOLUENESULFONATE

INTRODUCTION

A rather extensive study of the hydrolysis of *sec*-butyl *p*-toluenesulfonate has already been presented[1]. Before describing a new series of experiments, we propose to review briefly the motives which brought up this investigation.

According to current theory, two different mechanisms commonly occur for the nucleophilic displacement reactions. One is the unimolecular (S_N1) or ionization process, kinetically first order and which in the particular case of hydrolysis can be represented as follows:

$$R - X \xrightarrow{k_1} R^+ + X^-$$

$$R^+ + HOH \longrightarrow R - OH + H^+$$

Where k_1 is the first order rate constant, R^+ represents a carbonium ion and X^- a nucleophilic group. The driving force of such a reaction is the solvation energy of the two ions or that of the dipole which is formed before ionization is complete[2].

The other mechanism is the bimolecular substitution or displacement process, (S_N2), usually showing second order kinetics and giving rise to "Walden Inversion" when the X group is attached to an asymmetric carbon atom:

$$HOH + R\text{-}X \xrightarrow{k_2} H^+ + HO\text{-}R + X^-$$

In the particular case of hydrolysis shown above, the kinetics are first order if the reaction is carried out in aqueous solvents. k_2 represents the second order specific rate constant. The principal driving force now is the formation of a covalent bond between the attacking water molecule and the dipole R-X(3).

In general the first mechanism dominates in the reactions of tertiary halides and similar compounds while the second one prevails in the reactions of the primary derivatives. The secondary halides, occupying an intermediate position, show in some cases the characteristics of both mechanisms, whether simultaneously or when placed in different solvents. The isopropyl halides, for example, have been shown to hydrolyze not only through ionization to a carbonium ion but also by covalent interaction with solvent molecules. These compounds were thoroughly investigated by Hughes and Ingold(4). The sec-butyl halides, however, were only briefly studied by the same authors(5) and a few others(6). None of them however made use of optically active derivatives although some work was done with active sec-octyl halides(7).

The hydrolysis of p-toluenesulfonic esters has been studied less extensively than that of the organic halides. Some work was done in connection with sugar chemistry(8) but more important for our purpose is the work of Hammett and his

collaborators[9] on ethyl p-toluenesulfonate and 2,3-butanediol di-p-toluenesulfonate, and of Hughes, Ingold and their coworkers[10] on isopropyl p-bromo-benzenesulfonate. The behavior of these esters is quite similar to that of the corresponding halides although the large size of the p-toluenesulfonyl group lead us to think that some abnormal effect could eventually be observed in connection with the Walden Inversion.

For these reasons, we decided to study the hydrolysis of sec-butyl p-toluenesulfonate in an attempt to elucidate the complications arising from the simultaneous occurrence of both the uni- and the bimolecular mechanisms.

INTERPRETATION OF PREVIOUS RESULTS (1)

The results of our first investigations, although quite encouraging, were not entirely satisfactory. The hydrolyses were carried out in various solvent mixtures of water and acetone, water and dioxane and others. The rate was always first order. The ionic strength and mass-law effects which, according to Hughes and Ingold[10c] are good criteria for the determination of the mechanism of hydrolysis, were so small that no safe conclusion could be drawn from their study. The hydroxyl ion effect was not too clearly defined; no second order kinetics were detected like in the hydrolysis of methyl and ethyl halides[11] but there was some resemblance however with the alkaline hydrolysis of ethyl p-toluenesulfonate[9a].

The solvent effect was considerably more gratifying and in complete agreement with the current theory of dipole-dipole interaction[12,13]. It was found that the first order specific rate constant of hydrolysis fitted exactly the equation:

$$\log k_1 = \log k_1^o + \frac{B}{T} \frac{D - 1}{2D + 1} \qquad \text{eq.1}$$

Here D is the dielectric constant, k_1^o is the specific rate constant in the standard state of reference (zero ionic strength and vacuum: $D_o = 1$) and B is a function of the electric moments and radii of the dipoles involved in the reactions. (See page 8 for a complete definition.) B can be considered to be approximately constant for a given compound at a given temperature. The most interesting observation was that the term B, determined by measuring the slope in a plot of $\log.k_1$ *vs* $(D - 1)/(2D + 1)$, showed two distinct constant values for *sec*-butyl *p*-toluenesulfonate instead of only one like the tertiary halides or methyl and ethyl halides. In Table 1 are given some values of this B-factor for different esters. As can be seen from Table 1, tertiary halides all have high values for the B-factor while primary and secondary halides, although showing some variations, understandable since the nucleophilic character of the solvent plays an important role in their cases, all have B-factors lower than 30,000. The data found in the literature were never spread over a very broad range of dielectric strength. This might explain why the secondary halides have

TABLE 1

VALUES OF THE B-FACTOR FOR DIFFERENT ALKYL HALIDES

Ester	Solvent mixture		$B \times 10^{-3}$	Ref.
tert-Butyl chloride	Ethanol-water	25°	64.5	(14)
tert-Butyl bromide	"	25°	56.4	(14)
tert-Butyl bromide	Acetone-water	25°	52.0	(14)
sec-Butyl bromide	Ethanol-water	80°	8.80*	(16)(18)
Isopropyl chloride	"	80°	8.12	(4)(18)
Isopropyl bromide	"	55°	3.52	(4)(15)
n-Butyl bromide	"	59.4°	16.61	(14)
n-Butyl bromide	Methanol-water	59.4°	29.25	(14)
Ethyl bromide	Ethanol-water	70°	23.8	(17)
Ethyl bromide	Acetone-water	50.6°	3.56**	(19)
sec-Butyl tosylate	Acetone-water	30°	42.50	(1)
sec-Butyl tosylate	Dioxane-water	30°	37.00	(1) D>30
			7.0	(1) D<30

- -

* Based on values of the rate of hydrolysis of sec-butyl bromide and chloride, assuming the relation $k_1(RBr)/k_1(RCl)$ = 30/1 to be true here as it is in the case of the isopropyl and ethyl derivatives.

** In this case D was lower than 30; in all other cases, unless otherwise specified, D was higher than 30.

a solvent effect of the same order as the primary compounds. If the dielectric constant of the solvent mixture could be raised without affecting too much its nucleophilic tendencies, it is quite possible that the solvent effect would increase until it reaches values as high as that observed for the tertiary halides. Actually, Hughes and Ingold[19] claim that the change in the rate of solvolysis of isopropyl bromide with increase in the solvating power of the medium, is at first similar to the way normal halides behave, and finally resembles the behavior of tert-butyl bromide. (No data are given however.) This is indeed what we have observed for the hydrolysis of sec-butyl-p-toluenesulfonate, where the upper value of B, around 40,000, is not far from the values corresponding to the tertiary halides, while the B-factor in solvents of low dielectric strength is of the same order of magnitude as those for the primary and secondary derivatives. A similar observation is mentioned by Winstein and his coworkers[20], for isopropyl-p-bromobenzenesulfonate. These authors found that a plot of log k_1 vs their Y function, measuring the ionizing power of the solvent and in fact proportional to $D - 1/(2D + 1)$, was not linear and showed two distinct slopes, corresponding to those of tert-butyl and n-butyl bromides. Indeed the reason why a sec-butyl p-toluenesulfonate or p-bromobenzenesulfonate would show this effect for dielectric constant above 30 while the secondary halides do not show it even above 50 could be found in the high solvation energy of the p-toluenesulfonate and p-bromobenzenesulfonate groups, a factor which tends to favor the

unimolecular mechanism. The rate of hydrolysis of sec-butyl p-toluenesulfonate is more than one thousand times faster than that of sec-butyl bromide in the same solvent and at the same temperature (80% aqueous ethanol at 80°).

If one wants to go deeper into the dipole-dipole interaction theory, it will be seen that by development of a formula given by Kirkwood[21] for the free energy transfer of a strong dipole of moment m from a vacuum to a medium of dielectric constant D, assuming symmetrical distribution of charges in the molecule, one obtains the following equations for the term B, corresponding to uni- and bimolecular mechanisms[12,13]:

$$B_1 = -\frac{1}{k}\left[\frac{m_{RX}^2}{r_{RX}^2} - \frac{m_T^2}{r_T^3}\right] \qquad \text{eq. 2}$$

$$B_2 = -\frac{1}{k}\left[\frac{m_{RX}^2}{r_{RX}^3} + \frac{m_{H_2O}^2}{r_{H_2O}^3} - \frac{m_T^2}{r_T^3}\right] \qquad \text{eq. 3}$$

(RX represents any dipolar compound being hydrolyzed, and T stands for its transition state.)

These expression, like equation 1, page 5 are only valid at zero ionic strength and furthermore, the theory predicts possible abnormal behavior for dielectric constants lower than 25.

It is seen that B_2 will in general be smaller than B_1, since B_1 does not involve the term corresponding to a water

molecule and also because the transition state (‡) in a bimolecular displacement reaction has a smaller dipole moment than in the ionization mechanism.

This study of the solvent effect leads us to the following conclusions regarding the hydrolysis of sec-butyl p-toluenesulfonate:

1°, In solvents of dielectric constant above 30, the unimolecular mechanism is predominantly involved.

2°, In media of low solvation power, assuming that the previous equations still hold, the hydrolysis proceeds mostly if not entirely by the bimolecular mechanism.

In agreement with this, it was found[1] that the hydroxyl ion effect (increase of the rate of hydrolysis in the presence of a base) was more important in 80 per cent aqueous dioxane (20% water by weight; D = 11.5) than in 80 per cent aqueous acetone (D = 29.6) or than in 60 per cent aqueous dioxane (D = 25.5) where it was almost negligible. It was also observed that the first order rate of hydrolysis of sec-butyl p-toluenesulfonate is considerably higher than that of ethyl p-toluenesulfonate[9] (Table 2).

TABLE 2

Comparison of the rates of hydrolysis of sec-butyl and ethyl p-toluenesulfonate in 60% aqueous dioxane.

	T, °C	$k_1 \times 10^6$ (Sec^{-1})	Ref.
Sec-butyl Tosylate	30	8.2	(1)
Ethyl Tosylate	50	6.0	(9)

Since there is little doubt that the sec-butyl esters react more slowly by a bimolecular nucleophilic displacement process than the ethyl derivatives, another type of mechanism must have been involved in 60 per cent aqueous dioxane. It seems quite natural to assume that it is the ionization of the ester with formation of a so-called "carbonium ion".

The effect of addition of salts on the rate of hydrolysis of sec-butyl p-toluenesulfonate has already been discussed in some details in the first part of this work. Let us simply say here that both the effect of increasing the ionic strength and the effect of increasing the concentration of p-toluenesulfonate ions in the solution, although they do not support the conclusions drawn on the basis of solvent effects alone, are by no means opposed to them.

The last effect which remains to be investigated if one wants to follow the scheme proposed by Hughes and Ingold[3a] for the determination of the mechanism, is the stereochemical one[22]. After developing a new method of preparing optically active sec-butyl alcohol with a high degree of optical purity[23], we were able to obtain some optically active L(-)-sec-butyl p-toluenesulfonate and to follow the change of configuration of the butyl radical upon hydrolysis of the ester.

EXPERIMENTAL

Preparation of L(-)-sec-Butyl p-toluenesulfonate

This compound was obtained by the same procedure as described before[1], using optically active L(-)-sec-butyl alcohol obtained by the reduction of D(-)-2:3-butanediol according to a method described in another section of this thesis[23].

The final product, after a single purification by very slow freezing of the liquid over a period of two days and subsequent removal of the supernatant liquid, showed an observed rotation of α_D^{25}: -12.85°, $[\alpha]_D^{25}$: -11.30° . The last compares favorably with Kenyon and Phillips value[22]: $[\alpha]_D^{20}$: -11.10°.

The refractive index was measured: n_D^{25}: 1.5008 in good agreement with the value obtained previously for the purified DL product: n_D^{25}: 1.5009[1] and checking reasonably well with Kenyon and Phillips data: n_D^{13}: 1.5080[22].

Kinetic Experiments

Here again the previous procedure was followed[1]. Solvents: The dioxane was purified as recommended by Beste and Hammett[24]. It was refluxed over sodium hydroxide and, after filtration, refluxed over sodium, then distilled when needed. The acetone employed was C.P. Merck Acetone containing about 0.5% of water. The error introduced by this small amount of water is negligible in comparison with the

accuracy of the optical measurement method. The formamide used in some of the high dielectric strength solvent mixtures was C.P. Paragon. The distilled water added was always freshly boiled.

All the solutions were made up by volume. However, for the sake of conformity with the previous data, when it is referred to per cent aqueous acetone or dioxane, this means per cent by weight of acetone or dioxane.

The L(-)-sec-butyl p-toluenesulfonate was weighed out in small "weighing pigs" which were poured open into the solutions.

The runs were made in 25 and 50-ml. volumetric flasks. The sealed ampoule technique was found quite unnecessary when working at 30° except when the amount of olefin produced had to be determined. In that particular case, pyrex ampoules were used. A water bath kept at constant temperature was used as thermostat.

When the rate of formation of p-toluenesulfonic acid had to be followed, pipetted samples of the solution were titrated with standard 0.02 or 0.01 normal sodium hydroxide. Bromocresol purple was used as indicator.

All burettes and pipettes were calibrated.

The rotations were measured in 1 or 2 dm. tubes, in a Winkel-Zeiss polarimeter with its water jacket at 25°. Because of the slowness of the reaction, the time required for each reading at that temperature did not produce any

noticeable error when the rate of change of optical rotation had to be followed.

Olefin Determinations

The olefin analysis was done by the bromide-bromate[25] method in a 300-ml. flask with standard taper ground-in stopcock[26] and covered with a black cloth to exclude light. The connections were lubricated with a minimum amount of a paraffin oil-paraffin mixture having a low bromine blank. Sufficient bromide-bromate solution to furnish an excess 25 to 50 per cent over the amount needed was pipetted into the flask which was then evacuated. Then 5 ml. of 6 N sulfuric acid was run in followed, after an interval of 5 minutes, to allow time for bromine to be formed, by a 5-ml. sample of the solution to be analyzed, delivered from a pipette calibrated to contain[27]. The sample was washed thoroughly with about 20 ml. of water. The mixture was allowed to stand 5 minutes with occasional shaking. Then about 0.25 g. of iodate-free potassium iodide, freshly dissolved in water, was added. After shaking for 5 minutes, sufficient water was added to bring the volume to about 150 ml. The liberated iodine was titrated with 0.05 N sodium thiosulfate.

It was found that the water-dioxane medium itself uses up a considerable amount of bromine. To obviate this difficulty, blank titrations were run in each case with a solution of the final products of hydrolysis, in equivalent concentrations in the same solvent mixtures.

Before opening, the ampoules containing the solution were always cooled down in an iced water bath. The samples to be analyzed were pipetted directly from the ampoules, right after their opening.

RESULTS

Rate Determinations

A comparison of the rate obtained from measurements of the optical rotation with the rate of formation of p-toluenesulfonic acid can show whether the hydrolysis proceeds with inversion or retention of configuration.

A slight difficulty arose from the fact that the concentration of L(-)-sec-butyl p-toluenesulfonate had to be considerably higher for the rotation measurements than in the acidimetric titrations in order to permit reasonably good polarimetric readings. To this increase of the initial ester concentration corresponds a decrease of the specific rate constant. This was already mentioned in the first part of this work[1] and a curve was presented, showing the variation of the specific rate constant with the initial ester concentration, at 30° in 60 per cent aqueous dioxane (60% dioxane by weight). A straight line was obtained which could be extrapolated if necessary for higher values of the concentration.

A similar curve was drawn for the 80 per cent aqueous dioxane medium by plotting previous data[1] together with a newly determined value of the rate of hydrolysis. To obtain this last value, the rate was followed by the usual acid titration of a solution containing initially 0.179 mole of L(-)-sec-butyl p-toluenesulfonate per liter; the first order

specific rate constant determined graphically from a plot of 2.3 log. $a/(a - x)$ vs. time in seconds was: $k_1 = 0.80 \times 10^{-6}$ $sec.^{-1}$ at 30° C.

The variation of the specific rate constant with the initial ester concentration is therefore much smaller in this medium than in 60 per cent aqueous dioxane. We felt justified in assuming for the 70 per cent aqueous dioxane an intermediate value based on the respective values of the dielectric constant. The three curves obtained are shown in Figure 1. Under each of these a second surve has been calculated for the 61, 71 and 81 per cent aqueous dioxane solvents used in these experiments. The calculations were based on the relation between log k_1 and the function of the dielectric constant: $D - 1/2D + 1$.

The final results of the rate study are summarized in Table 3 for three different mixtures of dioxane and water. Under the heading k_1 are listed the first order specific rate constants, determined by following the production of p-toluenesulfonic acid during the hydrolysis, and recalculated, when necessary, to an initial ester concentration of 0.01 mle per liter. In the next column, k_1^* represents the same rate constant for higher concentrations of p-toluenesulfonate, obtained from the curves in Figure 1. The "optical rate" was derived from a plot of 2.3 log. α_o / α_t against time in seconds. Finally, k_1^{**} represents the slope of the curve: 2.3 log. $\alpha_o - \alpha_f / \alpha_t - \alpha_f$ versus time: α_o and α_f are the initial and final "observed" rotation and α_t is the rotation at time t. D indicates the dielectric constant of the medium.

TABLE 3

The Initial Rate of Hydrolysis of L(-)-sec-Butyl p-Toluenesulfonate at 30°, under neutral conditions, in different solvents (in $10^6 sec^{-1}$).

Solvent	D	Ester, M	k_1	k_1^*	k_1^{**}	Optical Rate	Optical Rate/k_1^{**}
61% aq. diox.	25	0.197	8.0	6.20	5.95	8.93[a]	1.50
71% aq. diox.	16.3	0.088	2.89	2.70	2.76	4.1	1.47
81% aq. diox.	11.1	0.179	0.88	0.80	0.75	1.2	1.60

a. Originally determined at an average temperature of 20°, calculated for 30° by using the activation energy estimated before: 22,320 cal/mole[1].

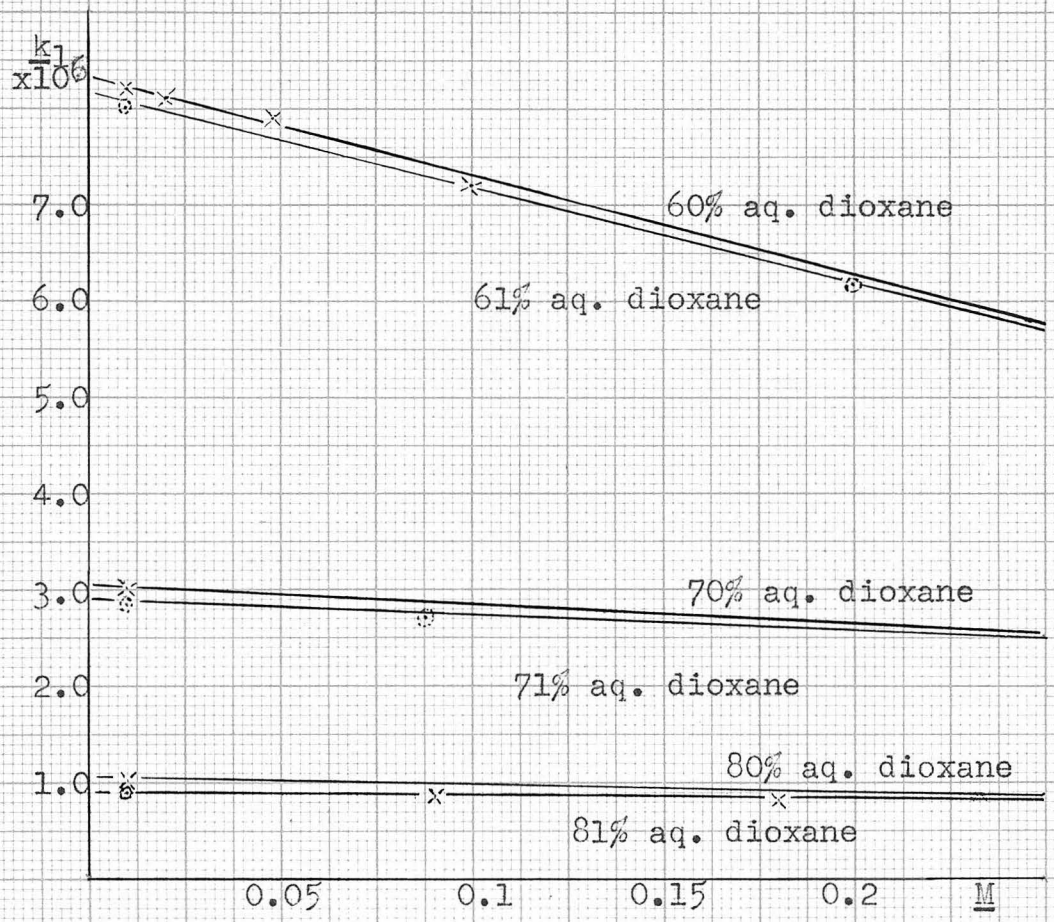

Fig. 1 - Variation of the First Order Specific Rate Constant with the Initial Concentration of sec-Butyl p-Toluenesulfonate in Different Mixtures of Water and Dioxane. -× Observed; ⊙ Calculated.

The concordance between the rate of acid production and the rate of decrease of the optical rotation, corrected for the opposite rotation of the D(+)sec-butyl alcohol formed during hydrolysis, is quite satisfactory. The "optical rate", considerably higher, clearly indicates than an inversion of configuration has occurred, at least to a large extent.

Tables 4 and 5 show the actual data for two of the experiments. Table 6 gives an example of the determination of the rate by titration of the increasing acidity of the solution. All this is summarised in Figures 2 and 3.

TABLE 4

Experiment No. 76: Rate of Hydrolysis of L(-)sec-Butyl p-Toluenesulfonate in 61% aq. dioxane, under neutral conditions.

Average Temp.: 20° Ester conc.: 0.197 m/l

Time in sec x 10^{+5}	α_t	$\log \alpha_o/\alpha_t$	Opt. rate x 10^6	$\alpha_t - \alpha_f$	$\log \frac{\alpha_o-\alpha_f}{\alpha_t-\alpha_f}$	k_1^{**} x 10^6 (sec-1)
0	-0.49	0.000	---	-0.64	0.000	---
0.470	-0.41	0.077	3.77	-0.56	0.059	2.89
0.595	-0.39	0.100	3.86	-0.54	0.074	2.86
1.475	-0.34	0.160	2.50	-0.49	0.116	1.81
1.583	-0.33	0.172	2.48	-0.48	0.125	1.82
1.864	-0.27	0.259	3.19	-0.42	0.183	2.26
2.212	-0.26	0.275	2.87	-0.41	0.193	2.02
3.25	-0.25	0.392	2.78	-0.40	0.205	1.45
4.52	-0.19	0.412	2.09	-0.34	0.275	1.40
5.31	-0.15	0.515	2.24	-0.30	0.329	1.42
6.05	-0.10	0.690	2.63	-0.25	0.408	1.56
10.37	-0.04	-----	----	-0.11	0.765	1.69
14.56	-0.09	-----	----	-0.06	1.028	1.63
17.37	-0.12	-----	----	-0.03	1.329	1.75
∞	-0.15		Av: 2.60	-0.00		Av: 1.89

By graphical differentiation, Opt. rate: 2.55×10^{-6} and k_1^{**}: 1.70×10^{-6}.

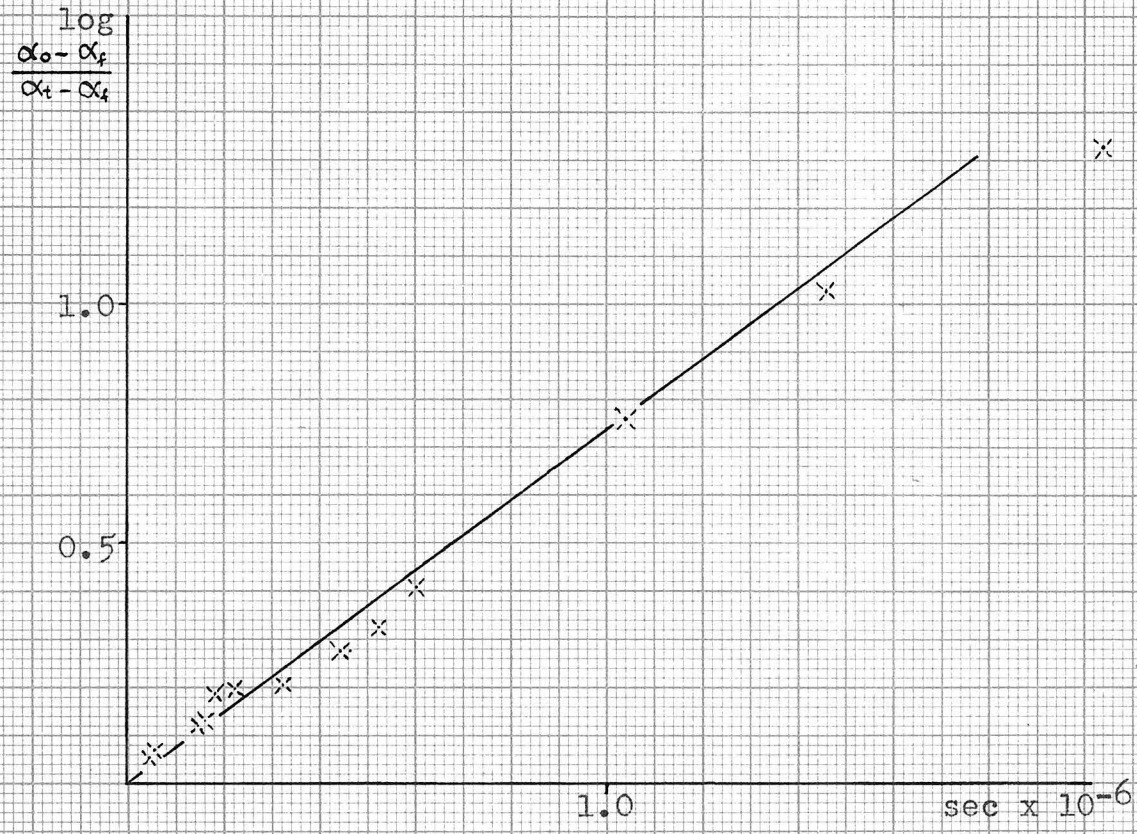

Fig. 2 - Experiment No. 76 - Rate of Hydrolysis of L(-)-sec-Butyl p-Toluenesulfonate in 61% Aqueous Dioxane, Under Neutral Conditions. $T_{av.}$ 20°.

TABLE 5

Experiment No. 78: Rate of Hydrolysis of L(-)sec-Butyl p-Toluenesulfonate in 81% of aq. dioxane, under neutral conditions.

Temp.; 30.0° Ester conc.; 0.179 mol/l

Time in sec 10^{+5}	α_t	$\log \alpha_o/\alpha_t$	Opt. rate	$\alpha_t - \alpha_f$	$\log \frac{\alpha_o - \alpha_f}{\alpha_t - \alpha_f}$	$k_1^{**} \times 10^{-7}$ (sec^{-1})
0.0	-0.42	0.000	---	-0.57	0.000	---
0.703	-0.39	0.032	1.03	-0.54	0.023	7.51
0.68	-0.35	0.080	1.09	-0.50	0.057	7.80
2.54	-0.31	0.133	1.21	-0.46	0.094	7.51
3.62	-0.29	0.162	1.03	-0.44	0.112	7.15
6.00	-0.25	0.225	0.87	-0.40	0.154	5.69
9.21	-0.10	0.626	1.61	-0.25	0.358	8.93
12.96	-0.02	1.322	(2.88)	-0.17	0.525	9.35
∞	-0.15		Av: 1.14	-0.00		Av: 7.705

The value marked in parenthesis is doubtful. By graphical differentiation, Opt. rate: 1.20×10^{-6} and k_1^{**}: 0.75×10^{-6}.

TABLE 6

Experiment No. 93: Rate of Hydrolysis of L(-)-sec-Butyl p-Toluenesulfonate in 81% aq. dioxane, under neutral conditions.

Temp.; 30.0° Ester conc.; 0.178mol/l Std. NaOH sol.; 0.09756 N Samples; 2 ml.

Time in sec 10^{+5}	ml NaOH /2ml sple	$\frac{x}{M}$	$\frac{a-x}{M}$	log $\frac{a}{a-x}$	k_1^* x 10^{-7} /sec
0.00	0.00	0.00	0.178	0.000	---
15.65	0.41	0.020	0.158	0.052	7.64
24.30	0.61	0.030	0.148	0.080	7.56
26.90	0.70	0.035	0.143	0.096	8.20
33.00	0.833	0.041	0.137	0.114	7.95
35.40	0.89	0.044	0.134	0.124	8.05
46.30	1.075	0.053	0.125	0.154	7.65
51.70	1.20	0.059	0.119	0.175	7.80

Av.: 7.835

By graphical differentiation, $k_1^* = 0.80 \times 10^{-6}$ sec^{-1}.

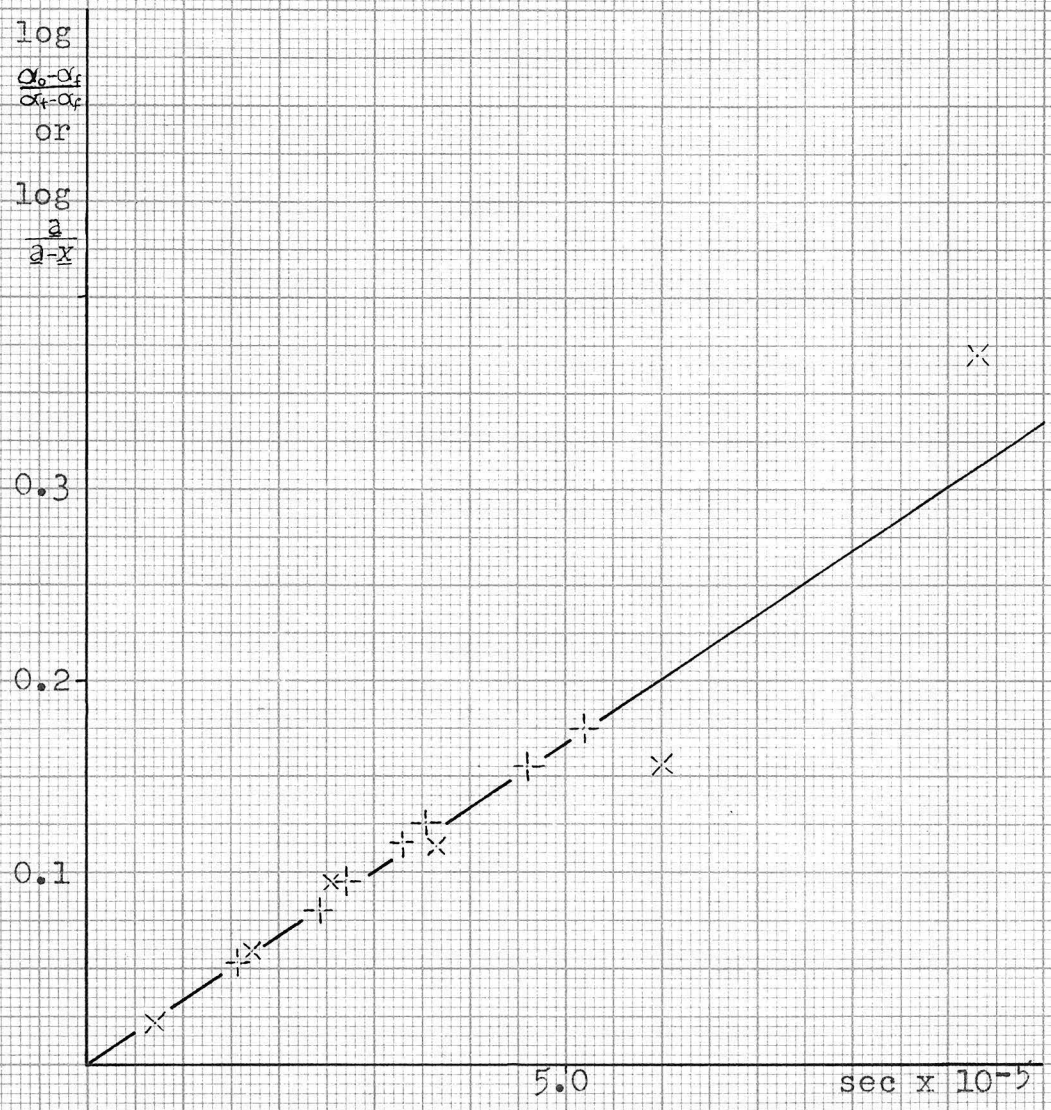

Fig. 3 - Experiments No.s 78 and 93 - Rate of Hydrolysis of L(-)-sec-Butyl p-Toluenesulfonate in 81% Aqueous Dioxane, Under Neutral Conditions, at 30°. × Polarimetric Rate (Table 5) + Acidimetric Rate (Table 6).

Optical Rotations of the Solutions after Complete Hydrolysis

As stated before, a recovery of the optically active alcohol was unfortunately quite impractical. A mere distillation of the final solution gives a ternary mixture, the boiling point of which is so close to that of the binary azeotrope of water and dioxane that no fractionation was possible. Elimination of the water by alternate distillation and careful drying gave a solution of 2-butanol in dioxane. The rotation was slightly improved, due to the higher concentration but the improvement was too small to justify the extra work. Even on very slow distillation of this solution through a small column it was found quite impossible to separate the 2-butanol from the dioxane (proportions: 1/200).

We had therefore to confine ourselves to the reading of the rotation of the final solutions. This unfortunately is not very accurate and consequently the following data (Table 7) are not to be taken as absolute but merely as part of a trend which they present as a whole.

After it was shown the amount of olefin formed was very small, even in 80% aqueous dioxane, it was possible to calculate in each case a value for the specific rotation. In doing this it was assumed that no other by-product could be formed: the amount of alcohol was therefore calculated from the initial concentration of p-toluenesulfonate.

These calculated values of the specific rotations were then compared with similar values for the optically pure alcohol. Parallel experiments were run with equivalent

amounts of active alcohol and equivalent amounts of p-toluene-sulfonic acid in place of active esters. Thus the rotations of the hydrolysis products were determined in solutions essentially identical with those of the optically pure alcohol. All these data are summarised in Table 7.

TABLE 7

Solvent Influence upon the Amount of Optical Inversion on Hydrolysis of L(-)sec-Butyl p-Toluenesulfonate under neutral conditions, at 30.0° C.

Solvent:	D	ester[a] M	α_D^{25}[b]	$[\alpha]_D^{25}$[b]	$[\alpha]_D^{25}$(alc)[c]	%Inv.	%olef.
20% aq. Dioxane	54[f]	0.087	-0.05	-7.4	-9.6	77	---
F:D:W 4:4:2[d]	52[f]	0.175	-0.17	-12.6	-14.5	87	---
F:D:W: 2:4:4[e]	50	0.179	-0.13	-9.6	-11.3	84	---
55% aq. acetone	45	0.089	-0.08	-11.8	-14.8	79	---
61% aq. dioxane	25	0.197	-0.15	-10.1	-11.2	90	0
71% aq. dioxane	16.3	0.088	-0.07	-9.6	-11.6	83	---
81% aq. dioxane	11.1	0.179	-0.15	-11.1	-11.9	93	---
81% aq. dioxane	11.1	0.178	-0.15	-11.1	11.9	93	1.5-2.0

a) initial ester concentration; b) "observed" and "specific" optical rotation after complete hydrolysis; c) optical rotation of L(-)sec-Butyl alcohol under identical conditions;
d) Formamide: 40%, Dioxane: 40%, Water: 20% (by volume);
e) Formamide: 20%, Dioxane: 40%, Water: 40% (by volume);
f) Calculated by approximation.

DISCUSSION

It is usually believed that the occurrence of a Walden inversion in a reaction indicates a bimolecular displacement mechanism. The entering nucleophilic ion or molecule attacks the back-side of the asymmetric carbon atom which changes its configuration while the original group is "pushed away".

The unimolecular, "ionic" mechanism on the contrary should be immediately recognizable when the reaction leads to complete racemization of the asymmetric center with loss of all optical activity.

This however is a hypothetical case which is rather seldom encountered. In general, an ionic mechanism leads to partial racemization with more or less inversion of configuration. In a very few cases, it even seems to lead to racemization with retention of configuration.

Ogg and Polanyi[28] have explained the first of these peculiarities by assuming that, when the life of the carbonium ion is of the same order as the oscillation frequency of the original C-X bond, the leaving X-group will prevent to some extent frontal attack by the solvent molecules and some inversion of configuration will result. It is certain that if this is true, the size of the leaving group is not without importance.

We believe that this is what happens in the hydrolysis of sec-butyl p-toluenesulfonate. First of all, the sec-butyl carbonium ion is certainly not very stable; the sec-butyl

and iso-propyl derivatives have much slower rates of hydrolysis than the tert-butyl derivatives which indicates only a small tendency for a carbonium ion to be formed. It is therefore quite likely that as soon as formed, the carbonium ion reacts with the solvent molecules and this occurs while the departing group (here the p-toluenesulfonic group) is still close enough to protect the front side of the asymmetric carbon atom from a solvent attack.

It is seen from Table 7 that L(-)sec-butyl p-toluenesulfonate is hydrolyzed with almost complete inversion of configuration, even in media of relatively high dielectric constant like the mixtures "formamide-dioxane-water" or even in 20 per cent aqueous dioxane (80% water by weight). Actually, asfar as we know, there is no record in the literature of a p-toluenesulfonate ester being hydrolyzed with complete racemization of configuration (at least, in the absence of any neighboring group participation).

A look at Table 7 will show that an increase of the dielectric strength of the solvent is accompanied by a small but constant decrease in the amount of inversion. This is well indicated in Figure 4 where it will also be seen that the amount of racemization increases with higher dilutions of p-toluenesulfonic ester. It is possible that this observation is related to the increase of the rate of hydrolysis with low initial concentrations of the ester.

According to Hughes[29], a decrease of the dielectric constant of the medium should bring about an increase of

of racemization when the unimolecular mechanism alone is involved. The reason for this is, the carbonium ion has more time to assume the planar configuration which leads to racemization, because it reacts more slowly.

No similar restriction exists for the bimolecular mechanism; under any circumstances it must lead to inversion of configuration.

Therefore an increase of inversion with a drop in dielectric constant and therefore of solvation power of the medium must be due to the gradual participation of the bimolecular mechanism, in complete agreement with the conclusions drawn from a study of the solvent effect in previous experiments.

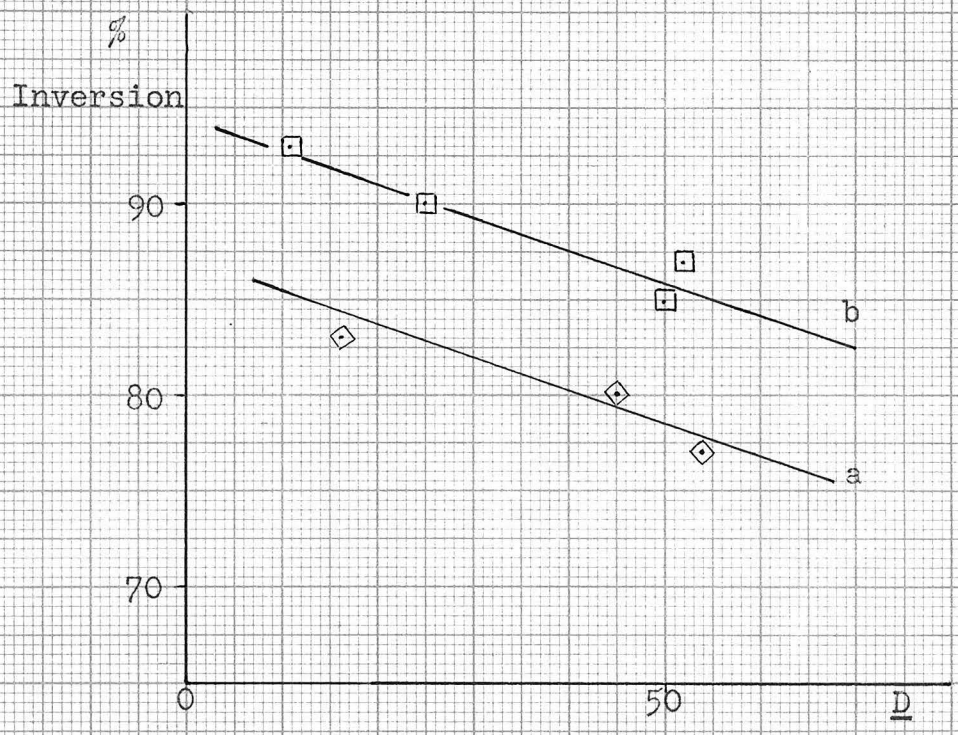

Fig. 4 - Effect of Increasing the Dielectric Strength of the Solvent upon the Amount of Optical Inversion during Hydrolysis of L(-) sec-Butyl -p-Toluenesulfonate.

a: initial ester concentration, 0.09 M.
b: initial ester concentration, 0.2 M.

CONCLUSIONS

These last observations together with those previously described and summarized in the introduction to this paper constitute another series of evidence in favor of the duality of mechanisms in the nucleophilic displacement reactions and more particularly in the solvolysis. The occurrence of a shift from unimolecular to bimolecular mechanism simply by decreasing the solvation power of the medium also indicates the intimate relation between both mechanisms. There is no sharp change but rather a gradual progression from one process to the other. As the dielectric strength of the solvent decreases, the driving force of the ionization mechanism, the solvation energy, becomes smaller and smaller while the reacting power of the solvent molecules is only slightly decreased. All this is in perfect agreement with the theories of Hughes and Ingold[2a]. It further demonstrates the primordial importance of the dielectric strength effect as a general solvent property, separate from any influence of a specific nature.

No quantitative determination of the participation of each mechanism has been attempted. The lack of accuracy in the work with the optically active derivative would have made this too speculative. Such an estimation however probably can be done if one is able to work under sufficiently extreme conditions so that each mechanism becomes actually singled out and can be studied separately.

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II. THE MECHANISM OF THE ACID AND BASE CATALYZED HYDROLYSIS OF D(+)threo-SODIUM 3-HYDROXY-sec-BUTYL SULFATE AND D(+)-2;3-BUTANEDIOL CYCLIC SULFATE.

THE MECHANISM OF ACID AND BASE HYDROLYSIS OF D(+) SODIUM 3-HYDROXY-sec-BUTYL SULFATE

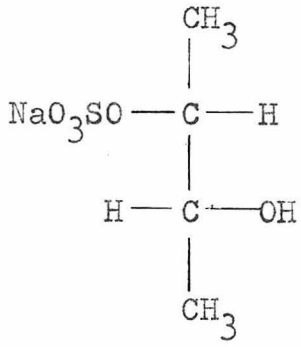
INTRODUCTION

In a recent publication, H. K. Garner and H. J. Lucas[1] described a method of preparation of D(+)-2;3-butanediol cyclic sulfate and the results of the acid and base catalyzed hydrolyses. They found that in the presence of acid, the meso-glycol was produced, while in the presence of alkali, a mixture of 80% DL, 5% D(-)- and 15% meso-2;3-butanediol resulted. Thus acid hydrolysis proceeded with an odd number of inversions, while alkaline hydrolysis proceeded mainly with an even number of inversions.

Garner and Lucas pointed out in the discussion of their paper the apparent contradiction between their results and those obtained by Burwell and Holmquist[2,3] on the hydrolysis of D(+)-sodium sec-butyl sulfate. These authors found that on acid hydrolysis, racemization occured to a very large extent (70%, ref. 2a) while in the presence of a base, L(-)-sec-butyl alcohol was produced with 94% inversion of configuration[3].

A different steric result does not necessarily imply a dissimilarity of reaction paths since the two sulfuric esters compared here possess a different number of asymmetric carbon atoms. On the other hand, similarity of stereochemical results ought not to be taken as evidence for an identity of mechanisms.

In order to correlate these apparently opposite results, we decided to investigate the hydrolysis of D(+)-sodium 3-hydroxy sec-butyl sulfate (I).



I

EXPERIMENTAL

D(-)-2;3-Butanediol:

The active glycol, product of the fermentation of starch with Aerobacillus polymyxa, was obtained from the Division of Applied Biology, National Research Council of Canada. It was distilled at 10 mm., b.p. 77.5-78°, α_D^{25} -12.92°, $[\alpha]_D^{25}$ -13.09°. Previous values for $[\alpha]_D^{25}$ found in the literature:[4 to 7] -13.0°, -13.19°, -13.34° and -12.85°.

D(+) Sodium 3-hydroxy-sec-butyl sulfate:

This was obtained from D(-)-2;3-butanediol by the method of Burwell and Holmquist[3,8], using the sulfur trioxide-dioxane reagent[9]. In order to obtain mainly the monosulfate, the reagent was added to the glycol rather than the reverse, as in the preparation of D(+)-sec-butyl sulfate.

28 G. (0.350 mole) of sulfur trioxide were distilled from 60 per cent fuming sulfuric acid, directly into a chilled mixture of 40 ml. of purified dioxane and 100 ml. of freshly distilled ethylene chloride. Efficient mechanical stirring was provided.

The use of a large amount of inert solvent was found necessary for two reasons: the first was to prevent charring which occurs quite easily, as soon as the reaction, which is strongly exothermic, goes out of control; the second was to bring the white crystalline sulfur trioxide-dioxane reagent into suspension, by shaking, just before pouring it slowly into 35 g. (0.389 mole) of D(-)-2;3-butanediol, diluted with

50 ml. of ethylene chloride. A cold water bath was used to prevent any overheating, which would have led to destruction of the glycol.

The resulting solution was then poured slowly over 35 g. of sodium bicarbonate dissolved in iced water. Finally the mixture was carefully neutralized with a small amount of diluted sulfuric acid.

The aqueous layer was separated and the solvent was evaporated at room temperature, in an air draft. The white residue was washed with several successive 20-ml. portions of ether and finally extracted in a Soxhlet apparatus with 150 ml. of methanol. The methanol solution was again evaporated and the residue was submitted to further extractions until no trace of sulfate ion could be detected in the residue after evaporation.

The solid was finally submitted to a six-step fractional crystallization from methanol until the head fractions showed the following optical rotations in methanol: $[\alpha]_D^{25}$ + 11.5° (c = 2.04) and $[\alpha]_D^{25}$ + 5.5° (c = 2.83). These rotations could not be improved by further recrystallizations.

The less soluble fraction showing an optical rotation of + 5.5° (17 g.) (22.5%) was identified as the D(+) sodium 3-hydroxy-sec-butyl sulfate. It had a saponification equivalent of 193.18 (theoretical: 192.2).

The dioxane used in the preparation of the reagent was purified by refluxing successively over sodium hydroxide pellets and sodium metal. It was distilled when needed from its mixture with sodium.

Kinetics

The rates of acid and base hydrolyses at room temperature were extremely slow; no special difficulty was encountered in handling the samples. The solutions were made up by weight; a small amount of salt was dissolved in water in a volumetric flask; then with the help of a siringe, approximately 10.5 ml. of the solution were transferred in a number of pyrex ampoules, drawn out of 18 mm. tubing. These ampoules were immediately sealed off and placed in an oil bath at constant temperature (81° and 100° C.).

For the rate determinations, an ampoule was removed from the bath at recorded time and immediately placed in iced water. After approximately 30 seconds, the contents of the ampoule had reached room temperature; the tip was broken, and a 10-ml. sample was removed with a calibrated pipette and titrated with 0.01 N sodium hydroxide, with phenolphthalein as indicator.

When a base was present the reaction mixture was first neutralized with an excess of 0.10 Nhydrochloric acid and then back titrated with 0.10 N sodium hydroxide.

In the case of the base catalyzed hydrolysis, better

results were obtained by using air-tight stainless steel vessels of 150 ml. capacity, made out of 1 inch diameter stainless steel pipe with screwed-in cap and lead gasket. Indeed, it was found that the reaction of the alkali with the pyrex glass of the ampoules was far from negligible at these temperatures.

For each titration, the entire vessel was removed from the oil bath, cooled down as rapidly as possible in iced water and, after shaking, a 10-ml. sample was pipetted out. The vessel was then put in boiling water for approximately one minute and finally placed back in the temperature-controlled oil bath. The whole operation required 3 to 4 minutes, for which a time correction was applied.

Rate Calculations

The specific rate constants were determined graphically by plotting $2.303 \log a/(a-x)$ or $\frac{2.303}{(b-a)} \log. (b-x)/(a-x)$ *vs.* time in seconds. In these expressions, a represents as usual the initial ester concentration and b the initial base concentration; x measures the amount of ester hydrolyzed.

When sulfuric acid and potassium bisulfate were added to the solution, the initial hydrogen ion concentration was calculated theoretically.

The mean activity coefficients for the perchloric acid solutions were taken from Landolt-Bernstein tables[10]. For the sulfuric acid solutions, they were determined from the data of Harned and Hamer[11] and according to the method of Lewis and Randall[12].

RESULTS

Acid Hydrolysis of D(+) Sodium 3-Hydroxy-sec-butyl Sulfate

The rate of hydrolysis was determined at 80° and 100° C. in aqueous solutions. One experiment was run in 70% aqueous dioxane (containing 30% water by weight). The ester concentration was always of the order of 0.01 mole per liter unless otherwise specified. Perchloric and sulfuric acids were used as catalysts, at concentrations varying between 0.05 and 0.15 mole per liter.

The reaction was found to follow a first order course when the acid concentration was at least five times as high as the ester concentration. When this ratio was lower, small deviations were observed after the hydrolysis was 50 to 60 per cent over.

Moreover, the specific first order rate constant was found to be almost exactly proportional to the activity of the hydrogen ions in the solution. This is shown by the data of the first two runs in Table 1.

Burwell[3] mentions a similar observation for the acid hydrolysis of sec-butyl sulfate and we have confirmed this in later experiments. Dreshel and Linhart[13] have observed the same relationship for ethyl sulfate.

In Table 1 are also shown some of the most important and most significant results obtained when sulfuric acid and a mixture of sulfuric and perchloric acids were used.

TABLE 1

ACID HYDROLYSIS OF D(+)SODIUM 3-HYDROXY sec-BUTYL SULFATE IN WATER AT 100° AND 80°

Ester M.	Acid	M.	Temp. °C.	$k_1 \times 10^6$ (sec^{-1})[a]	$[H^+]$	f_{H^+}[b]	$(k_1/a_{H^+}) \times 10^5$
0.01050	$HClO_4$	0.07636	100	36.2 ± 1.6	0.07636	0.812[c]	58.5
0.01042	$HClO_4$	0.1429	100	66.0 ± 3.0	0.1429	0.779[c]	59.2
0.01041	$HClO_4$	0.04808	81	3.97± 0.1	0.04808	0.826[c]	9.99
0.01041	H_2SO_4	0.02453	81	1.83± 0.1	0.0305[d]	0.86[e]	6.99
0.01048	$HClO_4$	0.04808	81	3.98± 0.3	0.0755[d]	0.89[e]	5.92
	$KHSO_4$	0.1956					

a) Initial first order rate constant; b) activity coefficients at 25°; no correction applied for higher temperature; c) see ref. 10; d) calculated theoretical value; e) see ref. 11 and 12.

The values of the ratio $\underline{k_1}/\underline{a_{H^+}}$ were calculated in order to obtain a specific rate constant independent of the hydrogen ion activity. Details concerning these calculations are given in the kinetics part, page 40. It can be seen that this ratio remains indeed a constant when the perchloric acid concentration is doubled, the temperature of course remaining the same. When however sulfuric acid is present, whether alone or together with perchloric acid $\underline{k_1}/\underline{a_{H^+}}$ is considerably decreased.

In table 2 and 3 and in Fig. 1 we present two typical determinations of the rate of acid hydrolysis in water.

TABLE 2

ACID HYDROLYSIS OF 3-HYDROXY-*sec*-BUTYL HYDROGEN SULFATE -- TYPICAL EXPERIMENT

Exp. No. 9 (61) -- Solvent, water. Temp., 81.0°. $[HClO_4]$ = 0.04808 M. $[HSO_4^-]$ = 0.1956 M. $[H^+]$ = 0.0755 N. Ester conc., 0.01048 M. Std. solution: NaOH, 0.1134 N.

Time (sec.)	NaOH ml[a]	$\frac{x,M}{x\ 10^3}$	$\frac{a-x,M}{x\ 10^3}$	$\log \frac{a}{a-x}$	$k_1 \times 10^6$ sec^{-1}
0	21.44	0	10.48	0	---
7500	21.50	.680	9.80	0.028	8.58
31800	56	1.360	9.12	.0595	4.31
54720	62	2.04	8.44	.0950	3.98
79900	64	2.27	8.21	.128	3.68
108000	76	3.63	6.85	.184	3.91
139800	84	4.55	5.93	.248	4.08
172800	90	5.22	5.26	.298	3.96
216600	98	6.03	4.45	.373	3.96
252000	22.04	6.80	3.68	.454	4.14

Average[b]: 4.00 ± 0.32

Graph. value: 3.98

- -

a) per 10.00 ml. sample; x is the concentration of acid formed in milimole per liter. b) not including the first value, obviously off.

TABLE 3

ACID HYDROLYSIS OF 3-HYDROXY-*sec*-BUTYL HYDROGEN SULFATE -- TYPICAL EXPERIMENT

Exp. No. 2 (55) -- Solvent, water. Temp., 100°
[$HClO_4$] = 0.07636 M. Ester conc., 0.01050 M.
Std. solution: KOH, 0.1046 N.

Time (sec.)	NaOH ml[a]	$\frac{a}{x}$, M $\times 10^3$	$\frac{a - x}{x}$, M $\times 10^3$	$\log \frac{a}{a - x}$	$k_1 \times 10^5$ sec^{-1}
0	7.30	0	10.50	0	---
13200	7.61	3.24	7.26	0.161	2.80
17400	7.76	4.81	5.69	0.266	3.52
19500	7.81	5.33	5.17	0.308	3.63
21600	7.84	5.65	4.85	0.335	3.56
42240	8.12	8.47	2.13	0.694	3.79
62400	8.20	9.41	1.09	0.984	3.63
73800	8.25	9.93	0.57	1.265	3.95

Average: 3.68 ± 0.16

Graph. value: 3.62

- -

a) See footnote at the bottom of Table 2.

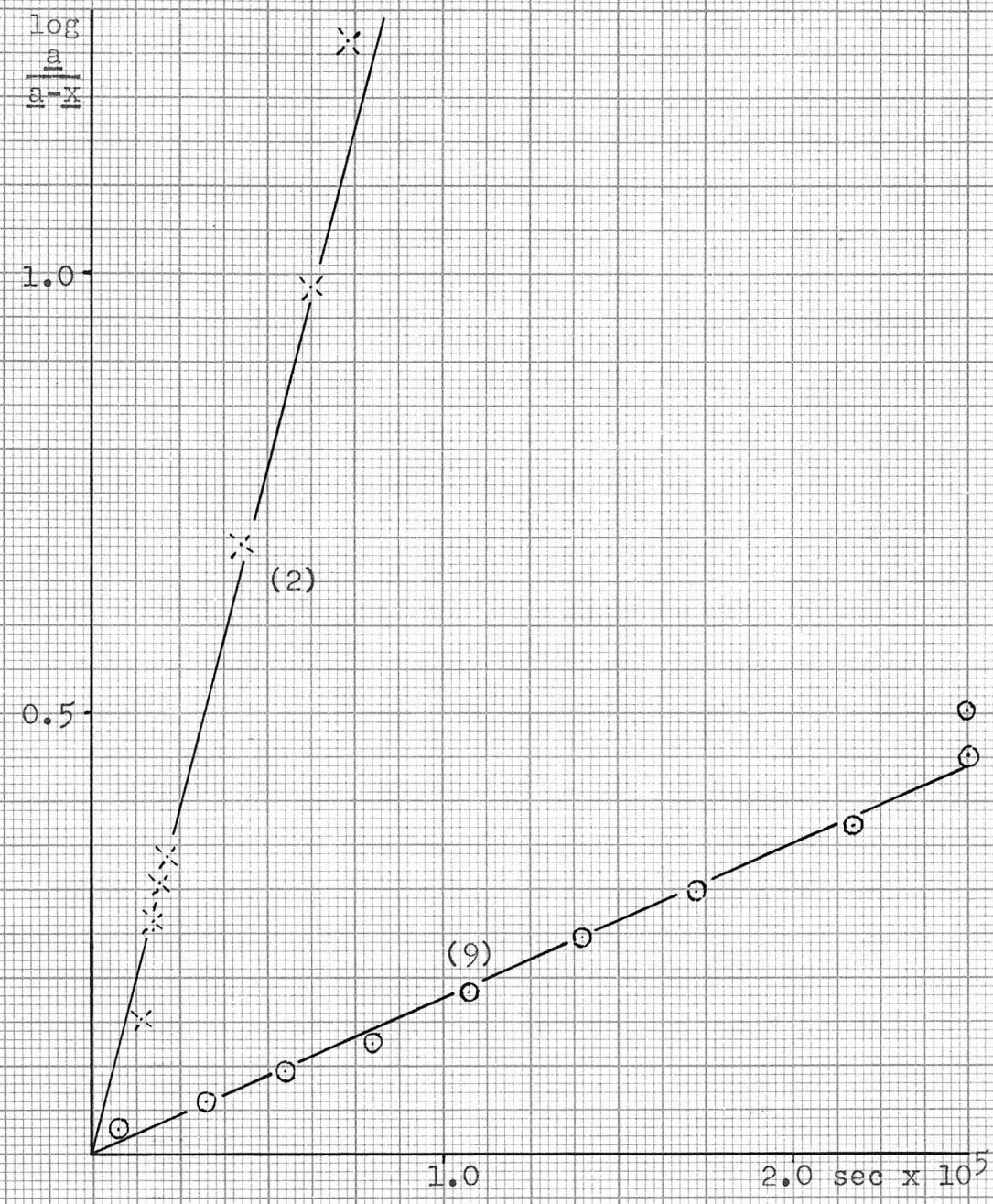


Fig. 1 - Acid Hydrolysis of 3-Hydroxy-sec-Butyl Hydrogen Sulfate. - Two Typical Experiments. (Data from Tables 2 and 3)

Once the rate of acid hydrolysis of D(+)-sodium 3-hydroxy-sec-butyl sulfate was determined, the next step consisted in the investigation of the stereochemistry of this reaction. In order to do this, we needed to be certain that the process of sulfation of D(-)-2;3-butanediol did not involve any racemization.

According to Burwell[8] the use of the dioxane-sulfur trioxide reagent for the sulfation of D(+)-2-butanol gave almost 100 per cent retention of configuration. We made use of the same reagent under the same conditions for the sulfation of D(-)-2;3-butanediol and we assume the same amount of retention. The absence of any appreciable amount of meso-2;3-butanediol among the products of acid hydrolysis seems to justify this assumption.

The method of Garner and Lucas[1] was used for the identification of the resulting glycol. The final solution was further acidified to make it approximately 1.0 N in acid and was then treated with paraformaldehyde; the cyclic formal of 2;3-butanediol was distilled over as soon as it was formed.

Since these authors have shown that configuration is retained in this step, it is possible to compare the properties of initial and final glycols merely by comparing the properties of their formals.

This is done in Table 4 in which previous data on the different formals are also given.

TABLE 4

PHYSICAL PROPERTIES OF THE CYCLIC FORMALS OF 2,3-BUTANEDIOL

Glycol (α_D^{25})	Added Electrolyte N	b.p.	mm	Formal n_D^{25}	α_D^{25} (°)
D[2](-12.93°)	---	96.0	748	1.3961	-23.54
meso[b] (0.00°)	---	101.5	748	1.4041	0.0
from hydrol. in water[c]	$HClO_4$, 0.0889	96.5	748	1.3958	-18.20
"	$HClO_4$, 0.148	96.0	748	---	-19.70
"	$HClO_4$, 0.970	---	---	1.3958	-24.0[d]
"	H^+ , 1.0 HSO_4^- , 2.0	96.5	748	1.3959	-15.2
from hydrol. in 70% aq. dioxane	$HClO_4$, 0.148	97.0	748	1.3959	-13.15
"	$HClO_4$, 0.148	96.5	748	1.3959	-12.62
from hydrol. in water	NaOH , 0.10	96.5	745	1.3959	-2.50

a) Previous values[(1)]: b.p. 95.6-95.9; n_D^{25} 1.3959 α_D^{25} -23.38°
b) M. Senkus, Ind. Eng. Chem., 38, 913 (1946).
c) The ester concentration was in all the cases, 0.235 M.
d) Approximate value (1.0°)

On the basis of the values of the refractive index and boiling point of the formal after acid hydrolysis, we conclude that practically no meso-2;3-butanediol is formed. Indeed, its presence would tend to increase the value of the refractive index. The properties of the DL-2;3-butanediol and its formal being identical with these of the active compounds, the product of acid hydrolysis in water must therefore be a mixture of D(-)- and DL-glycols, with 75 to 80 per cent of the former. When some potassium bisulfate was added to the solution, the activity of the formal was lowered. In a solvent mixture containing 70 weight per cent of dioxane and 30 per cent water, the activity of the final product was also considerably decreased.

The yields of formal were of the order of 80 to 85 per cent of the theoretical amount.

Basic Hydrolysis of D(+) Sodium 3-Hydroxy-sec-Butyl Sulfate

At 100°, the rate of hydrolysis under alkaline conditions was so fast that its accurate determination was impossible. We ran only a few experiments at 81°, and found the rate constant to be approximately first order. After the reaction had proceeded to about 80 to 85 per cent of its course, the rate dropped suddenly for unexplained reasons. The rate was also determined with better accuracy at 50° in order to determine the activation energy of the reaction. These results are given in Table 5.

TABLE 5

Basic Hydrolysis of D(+) Sodium 3-Hydroxy-sec-butyl Sulfate in Water at 80° and 50°.

Ester M	Base M	Temp. °C	$k_2 \times 10^3$ (sec^{-1}mole^{-1})[a]	$k_1^o \times 10^4$ (sec^{-1})[a]
0.02600	0.05025	81°	14.5	7.5
0.01041	0.1046	81°		8.7
0.01006	0.09784	50°	1.53	1.42
0.006935	0.0680	81°		7.9
0.006935	0.0680	50°	1.50	1.325

a) Initial rate constants.

The determination of the optical activity of the resulting formal as well as its refractive index and its boiling point indicate that the corresponding glycol is again a mixture of D(-)- and D,L-2;3-butanediol (see Table 4). The amount of retention is now very small, approximately 10 per cent. We suspected this extensive racemization to be due to the formation of a cyclic epoxide of 2;3-butanediol. In order to verify our assumption, we attempted the isolation of this epoxide. The solution after complete hydrolysis under basic conditions and without being neutralized, was distilled through a fractionating column. A low boiling, highly volatile liquid was obtained. Its properties compare excellently with those of cis-2;3-epoxybutane;

	unknown intermediate	cis-2,3-epoxybutane	D(-)trans-2,3-epoxybutane
b.p., °C.	59.5	59.7	53.7
N_D^{25}	1.3832	1.3832[a]	1.3705
α_D^{25}	0.0°	0.0°	-47.23°

We also observed that after complete removal of the oxide from the solution, a certain amount of DL-formal was nevertheless obtained upon acidification and addition of paraformaldehyde and distillation. Although no accurate determination of the overall yield was attempted, it was estimated to be around 85 or 90 per cent of the theoretical amount. Of this, approximately 55 per cent were recovered as the oxide and 30 per cent as the formal.

DISCUSSION

Acid Hydrolysis

It was shown in the previous pages that the acid hydrolysis of D(+)-3-hydroxy-sec-butyl sulfate is proportional to the hydrogen ion activity of the solution. This result, in complete agreement with the observations of Burwell[3] and others[13], shows that the fixation of a proton on the sulfate group of the ester, with subsequent formation of the free acid sulfate, constitutes probably the first step of the hydrolytic process.

Although monoesters of sulfuric acid are usually considered as strong acids, the presence of a small amount of non-ionized molecules in perchloric and even in sulfuric acid solutions is almost certain. As the hydrolysis proceeds, more acid sulfate molecules are formed in order to satisfy the equilibrium conditions.

The sharp decrease in the ratio of K_1/a_{H^+} when sulfuric acid replaces perchloric acid as a catalyst, or when potassium bisulfate is added to a perchloric acid solution of the ester strongly points towards an ionic mechanism of hydrolysis.

According to Hughes and Ingold's theories of aliphatic substitution[14], the slow rate determining step of these, so-called "S_N1" reactions is the reversible ionization of an ester molecule into a carbonium ion and a nucleophilic negative ion. In the particular case of D(+) 3-hydroxy-sec-butyl sulfate, we can represent this as follows:

$$HO\text{-}C_4H_8\text{-}O\text{-}SO_3H \rightleftharpoons HO\text{-}C_4H_8^{+} + {}^{-}\!:O\text{-}SO_3H$$

One sees immediately that if an excess of bisulfate ions is present in the solution, the reverse reaction, the recombination of bisulfate and "carbonium" ions to form a new molecule of sulfuric ester will be considerably increased and the observed rate of hydrolysis will be slowed down.

This so-called "mass-law effect" is not limited to ionic reactions. The negatively charged bisulfate ion can also attack a molecule of glycol by nucleophilic displacement, with formation of a covalent bond on the back-side of the asymmetric carbon atom. This last reaction however is never very extensive and one can consider the "mass-law effect" to be more or less specific of an ionic type of mechanism.

That the hydrolysis of organic sulfates proceeds indeed through an ionic mechanism under acid conditions seems also to be indicated by the findings of Burwell and Holmquist[3], confirmed later in the thesis, that D(+) sec-butyl sulfate gives rise to an extensively racemized alcohol upon acid hydrolysis.

Whatever the precise mechanism, i.e., whether ionic or nucleophilic, the "mass-law effect" should produce, together with the observed lowering of the rate of hydrolysis, an extensive racemization or even inversion of configuration of the asymmetric carbon atom C-2 (Fig. page 56). This was not observed. No meso-glycol was found with the D(-)- and DL-2;3-butanediol. Instead as it was seen in the preceding

pages, a larger proportion of the inactive DL compound was obtained when bisulfate ion was present.

Until now we have neglected to consider in this discussion the presence of an α-hydroxyl group (hydroxyl group on carbon atom C-3) in the sulfuric ester molecule. The participation of this neighboring hydroxyl group in the process of hydrolysis must now be considered because in it lies probably the explanation of the rather peculiar behavior mentioned above.

The formation of as much as 25 per cent of DL-2;3-butanediol can only be explained if one assumes the transitory existence of an inactive cyclic intermediate. The most obvious one would be an oxonium compound of the type postulated by Winstein and Lucas[15] for the reaction of 2;3-epoxybutane with the hydrogen halides.

Such a compound, in contrast to the corresponding epoxide, is not easily formed at it appears reasonable to assume that it is the product of a participation of the neighboring hydroxyl group within the general solvolytic process rather than an independent nucleophilic attack by the hydroxyl group on the back side of carbon atom C-2. In other words we are dealing here with one of these concerted "push-pull" reactions, called termolecular by Swain[16] and polymolecular by Hammett[17]. The α-hydroxyl group is involved in the progressive formation of a covalent bond on the back-side of the adjacent carbon atom while one or more water molecules are "pulling away" the bisulfate group by solvating it.

The net kinetic result must be an increase in the rate of hydrolysis of 3-hydroxy-sec-butyl sulfate over that of sec-butyl sulfate. This was indeed observed and is shown in Table 7 where the values of $k_1/[H^+]$, independant of the hydrogen in concentration are compared.

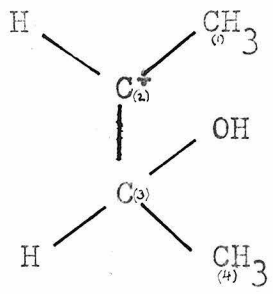
TABLE 7

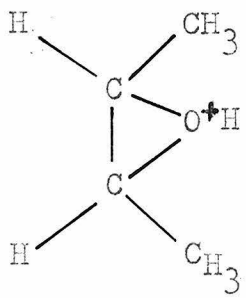
Comparison of the Rates of Hydrolysis of 3-Hydroxy-sec-Butyl Sulfate and sec-Butyl Sulfate in Water at 81°.

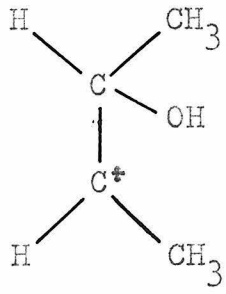
	Ester M	Acid M	k_1	$k_1/[H^+]$
3-hydroxy-sec-butyl sulfate	0.01041	0.04808	3.97×10^{-6}	8.3×10^{-5}
sec-butyl sulfate[a]	0.1002	0.244	1.22×10^{-5}	5.0×10^{-5}

a) See page 72 of this thesis.

The cyclic oxonium intermediate can be pictured as a resonance hybrid of at least the following three structures:

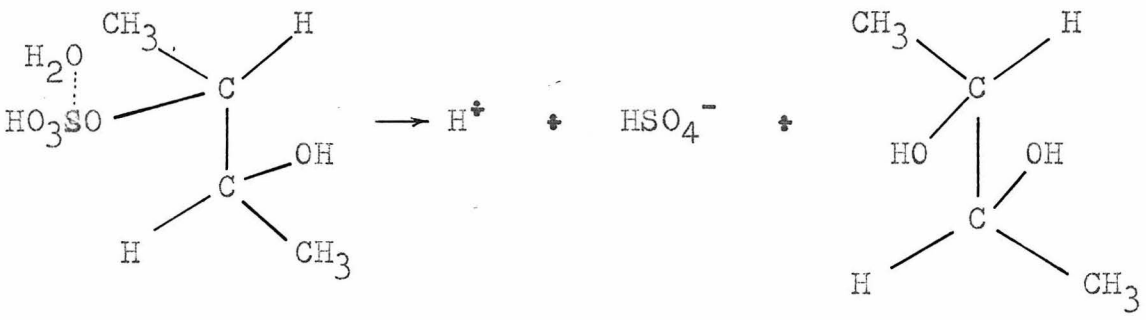






These clearly indicate that a straight-forward displacement mechanism, involving the attack by a water molecule on one of the asymmetric carbon atoms, leads to the optically inactive DL-2,3-butanediol.

The remaining 75 per cent of the recovered glycol shows retention of configuration. Similar observations in the chemistry of the carbohydrates[18] have been explained on the basis of an oxygen-sulfur bond fission. No evidence other than the retention of configuration itself was presented however, in favor of this assumption. The mechanism can easily be pictured. A water molecule attacks the sulfur atom which can momentarily expand its octet and the alkoxyl radical is simultaneously displaced:



If this oxygen-sulfur bond opening occurs, it can not however, represent the complete mechanism since it was shown that the alkyl-oxygen bond must be broken to permit the formation of an oxonium intermediate. Furthermore it has been demonstrated that no water molecule or bisulfate ion did attack the back-side of the asymmetric carbon atom C_2 since no meso-glycol was recovered at the end of the process.

Therefore the lowering of the rate as well as the increased racemization in the presence of an excess of bisulfate ions must have been due to frontal recombination between bisulfate ion and oxonium intermediate, with formation of DL-erythro-3-hydroxy-sec-butyl hydrogen sulfate.

The indications are therefore that at least two mechanisms are operating, one involving a nucleophilic displacement on sulfur, the other consisting in the intermediate formation of cyclic oxonium intermediate.

Obviously, the first mechanism leads to retention of configuration since the alkyl-oxygen bond is left undisturbed. It was shown above that the other mechanism must afford an inactive glycol.

If one can assume that these two processes are the only ones contributing to the hydrolytic process, their relative contribution should be indicated by the relative percentage of D(-) and DL formal recovered at the end of the reaction. Furthermore, if the nature of the solvent is profoundly altered, by adding a large amount of dioxane for example, one might expect a change in the relative contribution of each mechanism.

This was indeed observed. As indicated in Table 4, the optical activity of the formal recovered from an acid hydrolysis in 70% aqueous dioxane was considerably lower than when the hydrolysis was carried out in water.

An obvious explanation for this effect is found in the decrease of the concentration of water in the medium. Less water molecules are available for displacement on sulfur

while the formation of an oxonium ring is not appreciably affected and racemization becomes relatively more important.

Basic Hydrolysis

In comparison with the acid catalyzed reaction, the hydrolysis of D(+)-3-hydroxy-sec-butyl sulfate under basic conditions appears reasonably straightforward. DL-2,3-Butanediol is the main product of hydrolysis together with some excess of the D-form as indicated by the small retention of optical activity. This means that two Walden inversions have taken place.

The reaction mechanism was considerably clarified when it was possible to isolate a stable intermediate, identified as meso-2,3-epoxybutane. There is little doubt that the DL-glycol recovered as formal at the end of the process, is the product of hydrolysis of this inactive epoxide which in turn must have been formed from the hydroxy-sulfate by a mechanism similar to that proposed for the formation of a cyclic oxonium ion during acid hydrolysis.

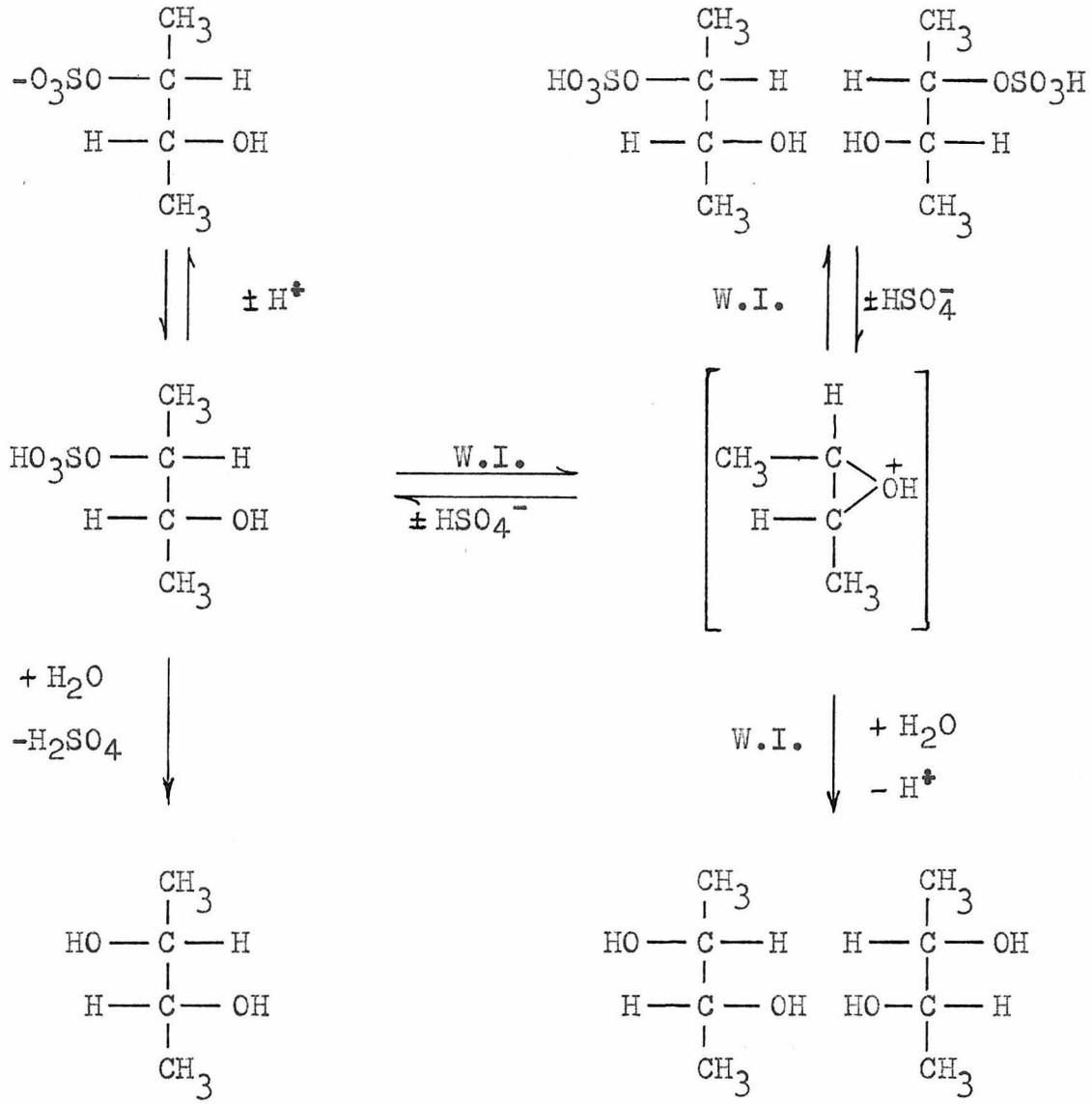
The α-hydroxyl ion group, formed in part from the hydroxyl group on C-3, under such strongly alkaline conditions, is constantly ready to "swing-in" as soon as the solvation forces have induced a sufficient electropositive charge on the neighboring carbon atom. In fact it helps in breaking loose the sulfate group by exerting its nucleophilic tendency to form a covalent bond on the back side of the asymmetric carbon atom.

Direct nuclophilic displacement by hydroxide ion does not seem to happen to any appreciable extent since no meso-glycol was recovered. This shows the extremely important

influence of the α-hydroxyl group in these reactions. Indeed Burwell[2] found that for D(+)-sec-butyl sulfate, back-side attack by hydroxide ion accompanied by a Walden inversion accounted for 94 per cent of the reaction. However, this process was rather slow since it involves an interaction between two negatively charged ions. Linhart[19] measured the rate of basic hydrolysis of methyl and ethyl hydrogen sulfate and found them to be very slow compared with the hydrolysis of neutral sulfate molecules like diethyl or dimethyl sulfate. He also observed second-order kinetics, the water molecules being not quite powerful enough to compete with hydroxide ions.

From our present results it appears therefore that a neighboring α-hydroxyl group is much more active in a nucleophilic displacement than the hydroxide ions surrounding the molecule in the solution. All these considerations do not eliminate the possibility of a displacement by hydroxide ions on the sulfur atom with subsequent opening of the oxygen-sulfur bond and retention of configuration. The 10 per cent excess of D-glycol which gives some optical activity to the recovered product can easily be accounted for on that basis.

In Figures 2 and 3, the complete scheme of acid and base hydrolyses have been summarized. The oxonium intermediate is marked between brackets to indicate its hypothetical nature.



D-(-) 2,3-Butanediol
75-80% in water
65% in 70% aq. dioxane

DL-2,3-Butanediol
20-25% in water
35% in 70% aq. dioxane

Fig. 2 - Acid Hydrolysis of D(-)-3-Hydroxy-sec-Butyl Hydrogen sulfate.

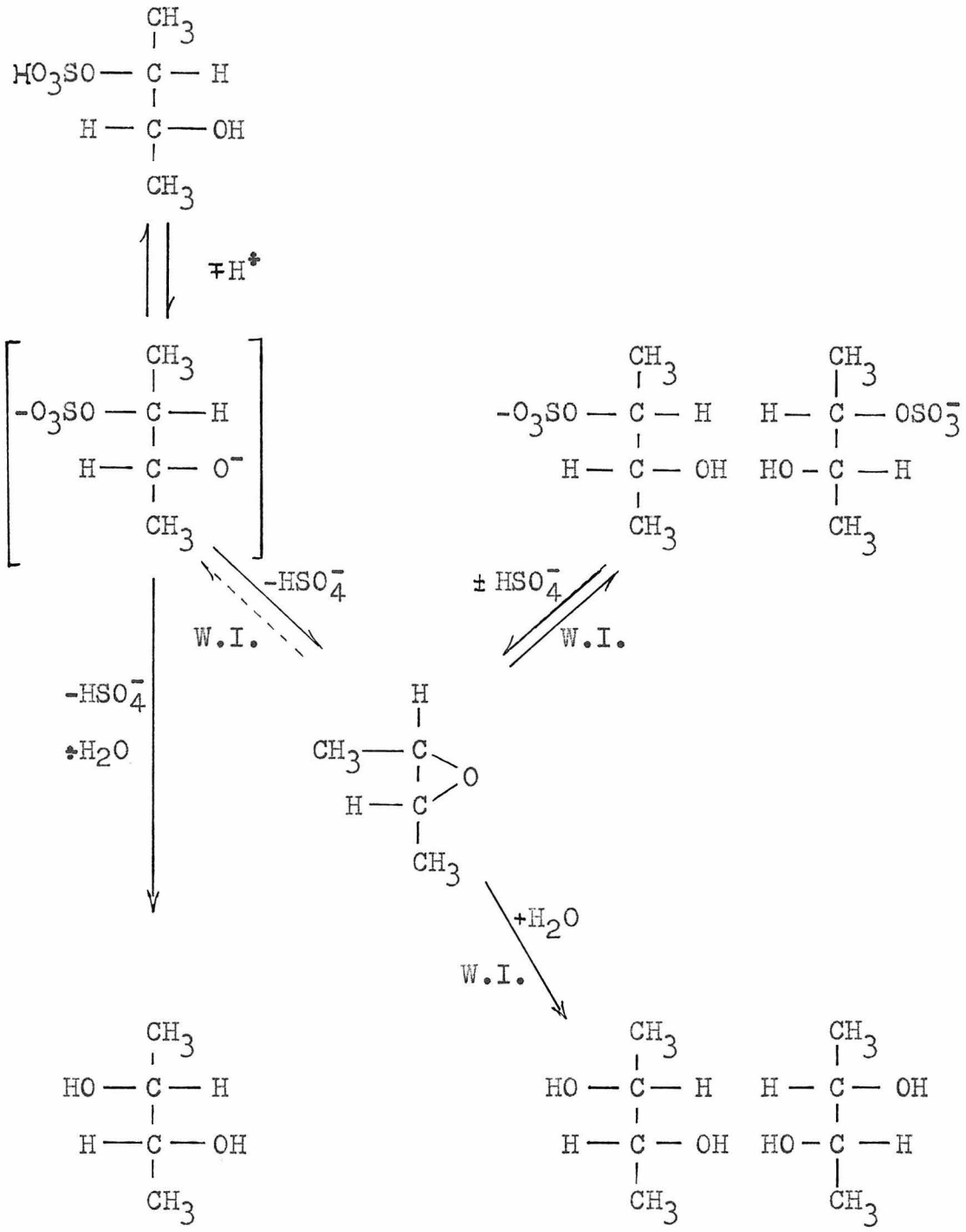


Fig. 3 - Base Hydrolysis of D-(-) 3-Hydroxy-sec-Butyl Hydrogen Sulfate

HYDROLYSIS OF D(+)-2;3-BUTANEDIOL CYCLIC SULFATE

One can assume with a reasonable amount of certainty that the first step in the hydrolysis of D(+)-2;3-butanediol cyclic sulfate, under acidic and basic conditions, is the opening of the heterocyclic ring and the formation of 3-hydroxy-sec-butyl sulfate. We have seen how this last compound behaves on further hydrolysis. We shall now try to correlate the results that Garner and Lucas[1] obtained with the cyclic derivative and our own observations, described in the preceding pages.

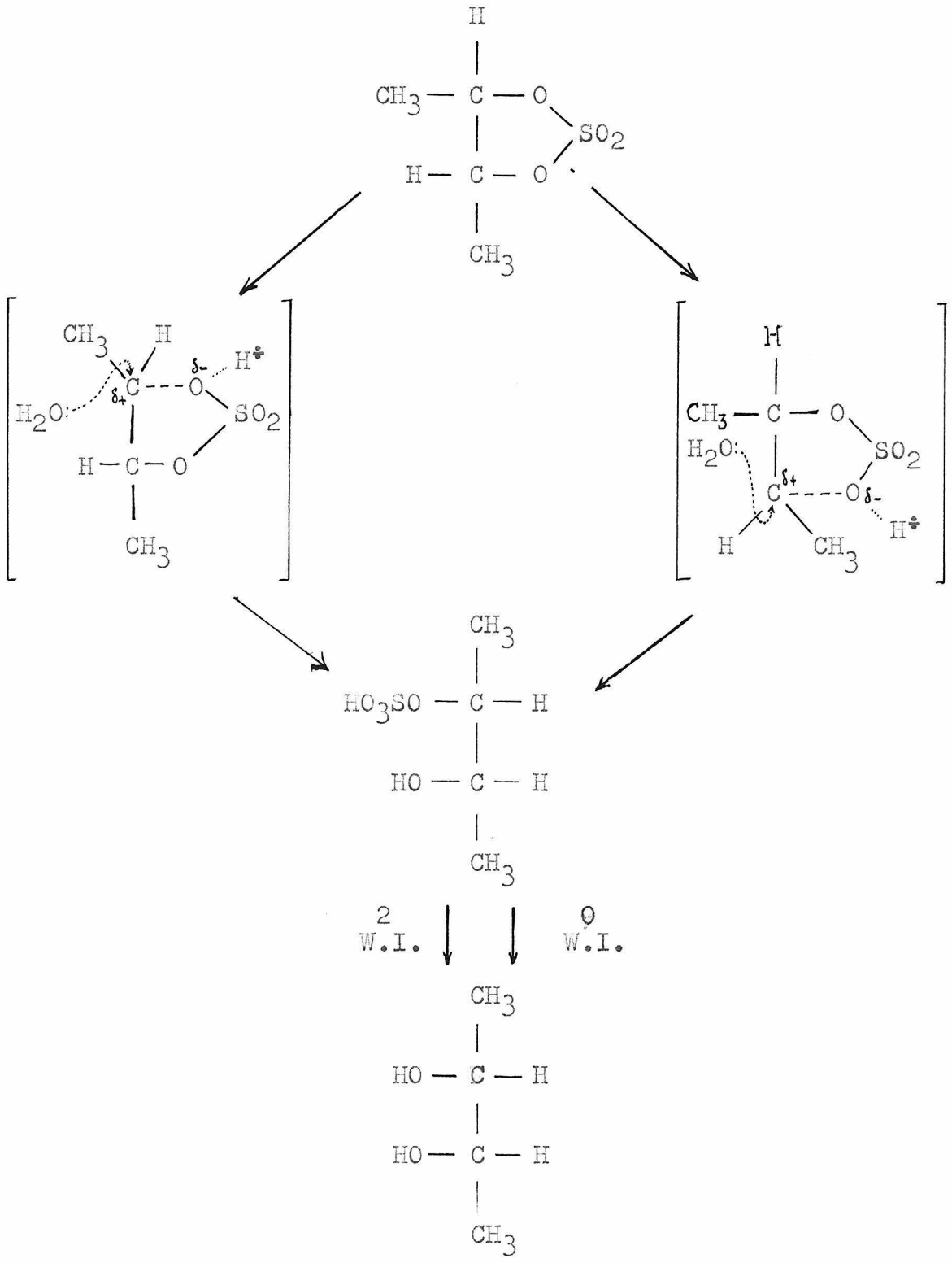
Acid Hydrolysis

We have shown that the acid hydrolysis of D(+)-3-hydroxy-sec-butyl sulfate takes place to a large extent with retention of configuration. A mechanism was pictured, involving an ionic intermediate, a sort of hybrid between an oxonium ion and a carbonium ion. The presence of an α-hydroxyl group was certainly an essential factor, not only in the ionization but also in the stabilization of the intermediate.

The cyclic sulfate however, does not possess any neighboring powerfully nucleophilic group. Ionization of one of the carbon-oxygen links can only occur when an "outsider", for example a water molecule, approaches and exerts its nucleophilic tendencies on the back side of one of the asymmetric carbon atoms. At the same time, a proton can help in the process by compensating for the negative charge induced on the sulfate group. This leads to a Walden inversion on one of the asymmetric carbon atom, giving L-erythro-3-hydroxy-

sec-butyl hydrogen sulfate, which on further hydrolysis, yields the meso-glycol with retention of configuration (Fig. 4). This is indeed what Garner and Lucas[1] observed on acid hydrolysis.

It is quite important to note that in this case, no opening of the sulfur-oxygen bond could have occurred since no DL-glycol was recovered. Yet, there was no electrostatic charge or anything which could have prevented it. When the ring is opened and the alkyl group is replaced by a proton, the positive formal charge on the sulfur atom may become sufficient to explain its interaction with the water molecules and the breaking of the oxygen-sulfur bond with retention of configuration.



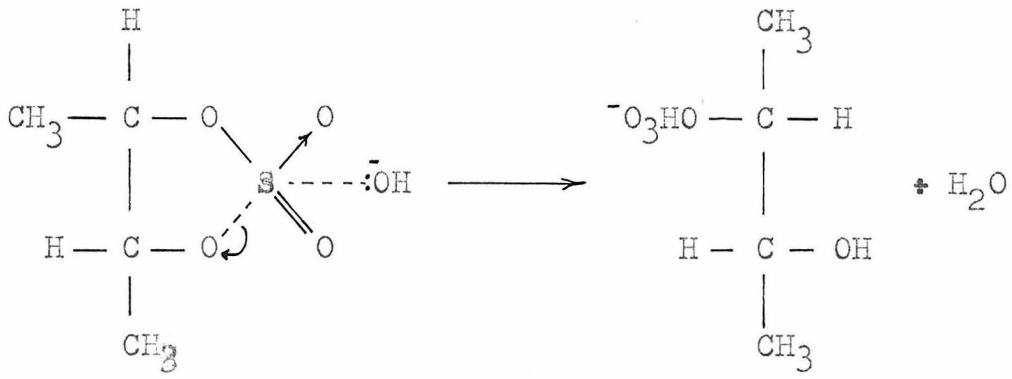
meso-2,3-Butanediol

Fig. 4 - Acid Hydrolysis of D(+)2,3-Butanediol Cyclic Sulfate

Basic Hydrolysis

Here on the contrary, it seems that the opening of one of the bonds between sulfur and oxygen atoms is the predominant mechanism. This is not too surprising however since hydroxide ions have a much stronger nucleophilic character than water molecules.

The absence of a negative charge on the sulfate group (like in the case of ionized acid sulfates) makes it easier for a hydroxide ion to reach the sulfur atom and cause rupture of an oxygen-sulfur bond.



Retention of configuration occurs with formation of D(+)-threo-3-hydroxy-sec-butyl sulfate. On further hydrolysis we have seen that this compound affords mostly the DL-glycol with some excess of the D-isomer (see page 59). The main reaction here is accompanied by two Walden inversions.

The possibility of an attack by hydroxyl ions on the back-side of the asymmetric carbon atoms of the cyclic sulfate can not be overlooked however. By a mechanism similar to that proposed for the acid hydrolysis, a hydroxyl ion

can open the ring, and through a Walden inversion form the DL-erythro-hydroxy-sulfate which, on further hydrolysis would yield the meso-glycol.

All this was noted by Lucas and Garner who observed that alkaline hydrolysis gave 80 per cent of DL-2;3-butanediol, with 5 per cent of the D-isomer and 15 per cent of the meso-glycol.* In Table 8 the quantitative data from our work as well as that of Garner and Lucas[1] have been collected.

- -

* Professor Lucas made the suggestion that the meso isomer could arise from an incomplete hydrolysis of cyclic sulfate, completed under acid conditions, when the formal is recovered.

TABLE 8

ACID AND BASE CATALYZED HYDROLYSIS OF D(+)-trans-2;3-BUTANEDIOL CYCLIC SULFATE: DL-erythro-3-HYDROXY-sec-BUTYL SULFATE AND D(+)-threo-3-HYDROXY-sec-BUTYL SULFATE

	Cyclic sulfate	No W.I.	Hydroxy-sulfate	No W.I.	Epoxide	No W.I.	Glycol	%
	D(+)trans-	1	DL-erythro	0	----------		meso-	100[a]
				1	?	1	meso	
Acid Hydrol.			D(+)threo-	0	**********		D(+)	75[b]
				1	?	1	DL	25[b]
	D(+)trans-	0	D(+)threo	0	----------		D(+)-	5[a]
				1	meso-	1	DL-	80[a]
		1	DL-erythro	1	DL-	1	meso-	15[a]
Base Hydrol.			D(+)threo	0	----------		D(+)-	10[b]
				1	meso	1	DL	90[b]

a) Lucas and Garner (Ref. 1); b) this Thesis.

SUMMARY AND CONCLUSIONS

The kinetics and the stereochemistry of the acid and base catalyzed hydrolyses of D(+)-3-hydroxy-sec-butyl sulfate have been described. On the basis of the results obtained a mechanism has been proposed in each case.

One has reached the conclusion that sulfuric esters are probably hydrolyzed by nucleophilic displacement both on the carbon and sulfur atom.

The preponderant retention of configuration and of optical purity on acid hydrolysis is probably due to a sulfur-oxygen bond opening. The racemization results from the intermediate formation of a cyclic epoxide or of an oxonium ion.

Making use of the assumption that the first step in the hydrolysis of 2:3-butanediol cyclic sulfate is the opening of the ring and the formation of 3-hydroxy-sec-butyl sulfate, a tentative explanation was given of the results obtained by Garner and Lucas with the cyclic compound. Although their quantitative results check reasonably well with ours, a serious difficulty was encountered in describing a mechanism for the opening of the sulfate ring.

We have not attempted to explain in any great detail why a water molecule causes the occurrence of a Walden inversion or why a hydroxide ion is capable of opening the sulfate ring with retention of configuration. Instead, we have briefly described what we believed is the most simple mechanism

which can account for these observations.

Before we can decide to what extent the opening of the sulfur-oxygen link takes place in both acidic and basic hydrolyses, we need more information about the solvolytic reactions of a simple alkyl sulfate like for example sec-butyl sulfate. This shall be the subject of the next section of this thesis.

On the kinetic point of view, we are confronted here with another example of what Swain calls a "concerted displacement" reaction. This is not however a termolecular process since the "pushing" action is internal and comes from the α-hydroxyl group. We refrain from calling it a bimolecular reaction since it is not known how many water molecules are actually involved in the solvation of the ionic intermediate.

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III. THE ACID AND BASE CATALYZED HYDROLYSES OF L(-)SODIUM sec-BUTYL SULFATE

THE ACID AND BASE CATALYZED HYDROLYSES OF L(-)SODIUM sec-BUTYL SULFATE

INTRODUCTION

The study of the acid and base catalyzed hydrolyses of D(+)-3-hydroxy-sec-butyl hydrogen sulfate was undertaken with the idea that it would furnish an interpretation of the rather unexpected results obtained by Lucas and Garner[1] with D(+)-2;3-butanediol cyclic sulfate[2].

During that study, however, our attention became focused on the apparently abnormal behavior of this ester which, on acid hydrolysis, yields a glycol of high optical activity and of configuration identical with that of the starting material.

Although this was not too surprising since a similar observation had already been made by Meth[3] who, in 1907, used the brucine salt of sec-butyl hydrogen sulfate to resolve the alcohol, and more recently by Burwell[4] who actually studied the hydrolysis of D(+)-sec-butyl hydrogen sulfate, it was nevertheless considered rather strange that an alkyl sulfate should behave so differently from a sulfonic ester under practically identical conditions.

The work of Burwell does not include any kinetic data and is rather indefinite as far as actual experimental conditions are concerned. We decided to repeat and extend his experiments and in particular to investigate the influence of a change of solvent on the relative extent of racemization during hydrolysis.

We also wanted to find in this new series of investigations a more definite answer to the problem with which we were confronted in the study of the hydrolysis of D(+)-3-hydroxy-sec-butyl hydrogen sulfate, i.e. how important is the participation of the α-hydroxyl group and to what extent a rupture of the sulfur-oxygen link is responsible for the high retention of optical activity of the final glycol.

Since our experiments are so closely connected with the work of Burwell and his collaborators, we believe that a short summary of the principal findings of these authors will be useful.

In 1942, Burwell[5] found the sec-butyl hydrogen sulfate, formed by reacting optically active 2-butanol and sulfuric acid, retains some optical activity. Starting from the observations of Robey[6] that a mixture of 2-butanol and sulfuric acid is actually an equilibrium involving butanol, sulfuric acid, sec-butyl hydrogen sulfate and the conjugate acid of 2-butanol,

$$2\ C_4H_9\text{-}OH + 3H_2SO_4 \longrightarrow C_4H_9\text{-}OSO_3H + C_4H_9\text{-}OH_2^+ + 2HSO_4^- + H_3O^+$$

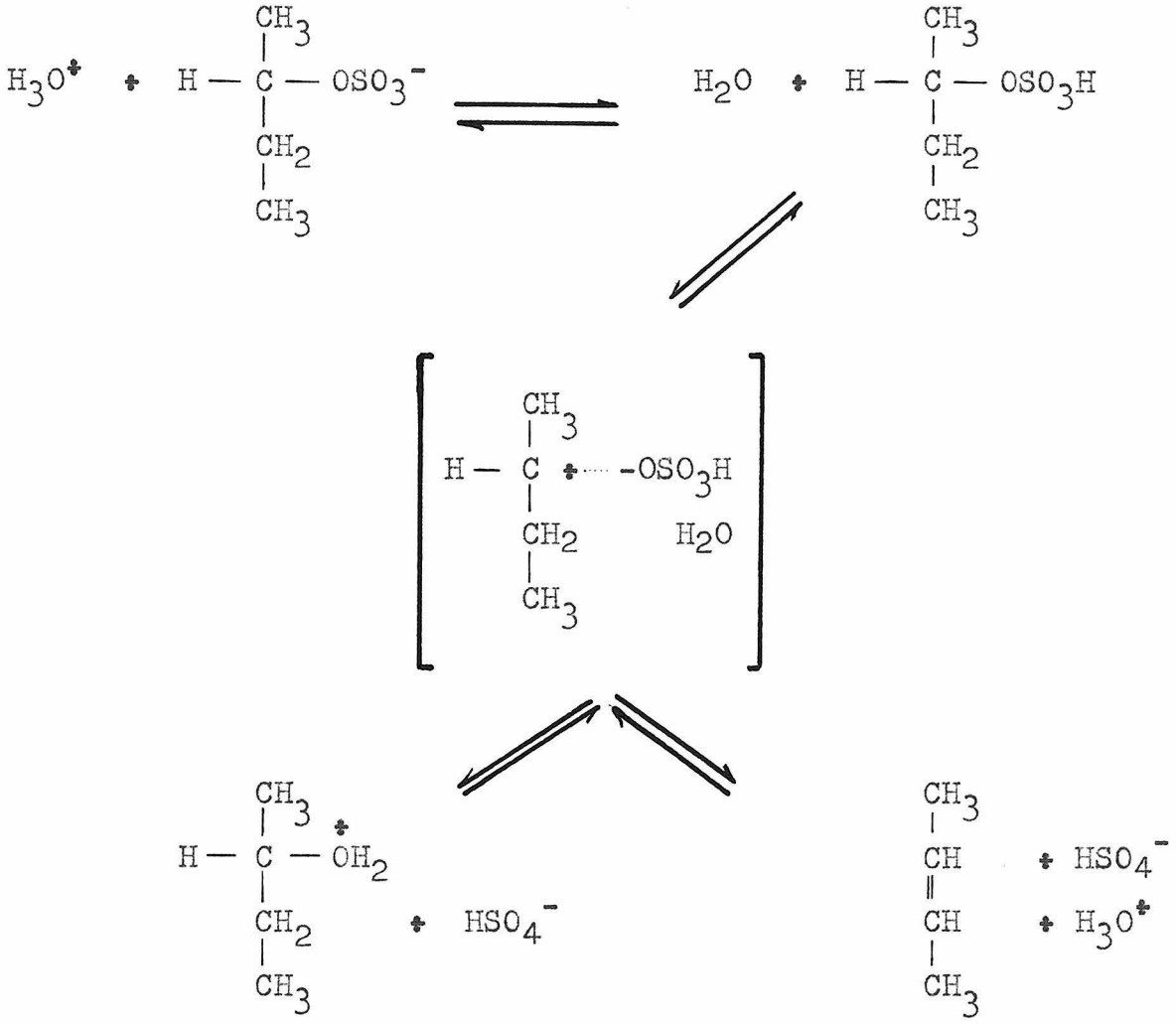
Burwell showed that the sulfation process can be correlated with all the other reactions which occur when 2-butanol and sulfuric acid are mixed together: butylene formation, dehydration, polymerization, formation of ether and direct racemization. For this, Burwell postulated the existence of a carbonium ion intermediate but he immediately insisted

on the fact that it was very dubious whether one should think of this ion as having any real, independent existence.

A few years later, the same author[4] prepared the barium salt of (+)-sec-butyl-hydrogen sulfate and, since this compound was obtained by the reaction between chlorosulfonic acid or sulfur trioxide in dioxane and D(+)-sec-butyl alcohol, he thought justified in assuming that it had the D configuration, the carbon-oxygen bond being not disturbed during this process.

He then studied the acid hydrolysis of this optically active ester and obtained an alcohol which had retained 30 per cent of its original rotation. The racemization was assumed at that time to have occumed entirely during the solvolysis and this was confirmed in later experiments. Although the conditions of hydrolysis are not clearly stated, it is evident that the reaction was carried out in relatively dilute solution, in the presence of approximately 1.0 N sulfuric acid. Some butylene was formed as one would have expected. The author also observed that neutral hydrolysis of sec-butyl hydrogen sulfate was almost negligible, even in boiling water; he concluded as others[7] had done before that the reacting species must be the free acid molecule.

By a careful study of the exchange reaction between sulfuric acid-D_2 and optically active 2-butanol, Burwell was then able to propose the following scheme which explains altogether the racemization of the alcohol, the evolution of butylene and the formation and hydrolysis of sec-butyl hydrogen sulfate:



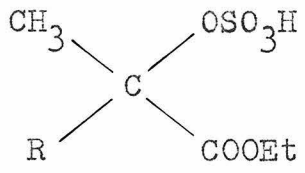
The comparison between the rate of racemization of the alcohol and the rate of deuterium exchange clearly indicates that each reaction is independent of the other. All the evidence is against the possibility that the olefin might be an intermediate between the alcohol and the sulfuric ester. There is less convincing proof that the ester is not an intermediate in the conversion of the alcohol to the olefin and vice-versa.

Again the author insisted on the fact that only partial racemization results from the intertransformation of alcohol and alkyl-sulfuric acid and that, consequently, the life of the carbonium ion pictured in the mechanism must be assumed to be very short.

Finally in a third paper, Burwell and Holmquist[8] investigated the alkaline hydrolysis of D(+)-sec-butyl sodium sulfate and showed that it took place with inversion of configuration. Even under the drastic conditions employed, the reaction is claimed to be relatively slow and this is understandable since it involves the interaction between two negatively charged ions.

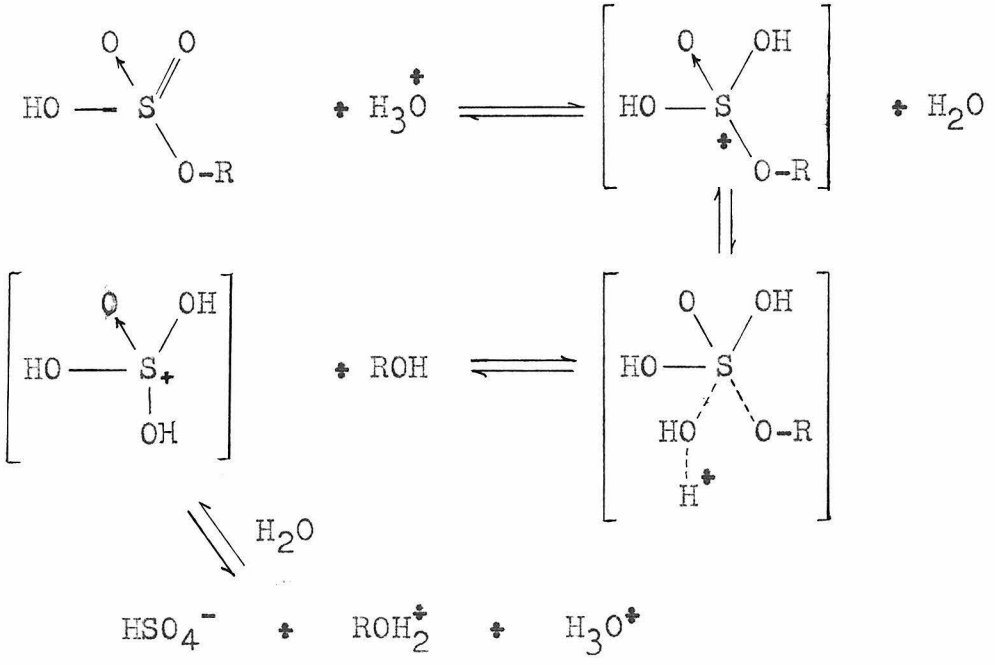
In all his work, Burwell never paid much attention to the possibility of a hydrolytic mechanism involving a nucleophilic displacement on the sulfur atom and the rupture of the sulfur-oxygen bond.

According to Suter[9] this sort of mechanism does not take place in the solvolysis of tertiary alkyl sulfates since these compounds are in general unstable and, in sulfuric acid, are dissociated into bisulfate and carbonium ions. As soon as the sulfuric acid solution is diluted with water, the alcohol is obtained. A further evidence that hydrolysis involves ionization in this case is found in the stabilization of the acid sulfate derivatives of α-hydroxy-α-methyl-carboxylic esters which have been isolated[10] as intermediates in the preparation of alkyl methacrylates:



Although the powerful electron attracting tendency of the carboxylic group is the polar character of the carbon-oxygen bond, it is evident that it does not have much effect on the oxygen-sulfur linkage.

In primary alkyl sulfates however, the bond between carbon and oxygen, like that between carbon and halogen in primary alkyl halides does not possess much polar character and is usually cleaved under the influence of a displacing nucleophilic reagent attacking the back-side of the carbon atom (Walden inversion). There is apparently no reason why the same sort of displacement could not take place on the sulfur atom as well:



An interesting case which seems to bring some strong evidence for this kind of mechanism is provided by neopentyl alcohol which, according to Whitmore and Rothrock[11], reacts with sulfuric acid without any rearrangement, to give neopentyl hydrogen sulfate. This compound, like the corresponding acetate[12], yields the original alcohol upon hydrolysis. What probably happens is that the usual back-side attack on the carbon atom, impossible here because of steric hindrance, is entirely replaced by a nucleophilic displacement on sulfur, leaving the carbon-oxygen bond undisturbed. In connection with this, it would be very interesting to know whether α-methyl allyl hydrogen sulfate, if it can be prepared, reacts in a similar fashion since the acetate[13], like neopentyl acetate, does not rearrange upon acid hydrolysis.

These few examples are given here in order to show that the mechanism of sulfuric ester formation and hydrolysis is still poorly understood today. The following study represents an attempt to clarify the problem.

sec-Butyl hydrogen sulfate was chosen, not only because it can be prepared optically active, but also because it is intermediate between the primary and tertiary derivatives. Moreover, also interesting is a comparison of its behavior with that of 3-hydroxy-sec-butyl hydrogen sulfate, for this might clarify the α-hydroxyl-neighboring group effect.

Alkaline hydrolysis was not studied since it has been shown by Burwell[8] that it gives complete inversion of

configuration and therefore eliminates any possibility of rupture of the sulfur-oxygen bond.

EXPERIMENTAL

L(-)-2-Butanol:

The optically active alcohol was obtained by reduction of D(+)2;3-butanediol, according to a new method described in another section of this thesis[15]. $[\alpha]^{25}_{D}$ -13.25°; b.p. 97.5°-98.0° (745mm); n^{25}_{D}: 1.3949;

L(-) Sodium sec-butyl sulfate:

This compound was obtained by the method of Burwell and Holmquist[8]. 15.5 g. of (0.194 mole) of sulfur trioxide were slowly distilled from 30% C.P. fuming sulfuric acid, into a chilled mixture of 30 ml. of freshly purified dioxane and 50 ml. of redistilled ethylene chloride, contained in a 250-ml. three-necked flask, fitted with a sealed mechanical stirrer and with an exit tube leading to a diluted aqueous solution of sodium hydroxide. Vigorous stirring was maintained during the whole operation. The apparatus was all-glass and the ground joints were lubricated with an especially unreactive fluorinated grease.

When the desired amount of sulfur trioxide had distilled into the reaction flask, the distilling end of the apparatus was disconnected and replaced by a separatory funnel; 14.3 g. (0.193 mole) of L(-)-2-butanol were then added dropwise while the white crystalline suspension of sulfur trioxide-dioxane reagent was vigorously stirred and kept below 15°.

After complete addition, the reacting mixture was allowed to warm up to room temperature and stirring was continued for half an hour.

The yellow solution was then poured slowly over 17 g. of sodium bicarbonate dissolved in iced water. The mixture was finally carefully neutralized (litmus) with a small amount of diluted sulfuric acid. The aqueous layer was separated and treated as explained before[16] for the preparation of 3-hydroxy-sec-butyl sodium sulfate. Once the white solid obtained by evaporation of the methanol extracts was freed from sodium sulfate, it was recrystallized from methanol and carefully dried.

Its optical rotation was measured: $[\alpha]^{25}_{D}$ -9.14° (c : 3.45 in water). Burwell and Holmquist calculated that the optically pure compound should have $[\alpha]^{25}_{D}$ -10.7°, on the assumption that the alcohol having $[\alpha]^{25}_{D}$ -13.64° (Pinckard and Kenyon[17]) was optically pure. Its neutralization equivalent was found to be 179.3 (theoretical: 176.18 or an error of 2%). Further purification was not attempted.

DL-Sodium sec-butyl sulfate

The inactive sulfate was prepared in an identical fashion starting from inactive 2-butanol (Eastman-Kodak, White label). The purification however was carried further and a compound having a neutralization equivalent of 176.5 was obtained.

Kinetics:

The rates of acid catalyzed hydrolysis were determined at 81° and 40° C. in water and various solvent mixtures of water and dioxane. The sealed ampoule technique already described[18], was used when the reaction was carried out at 81°. At 40°, the solution were kept in 50 and 100-ml. glass-stoppered graduate cylinders. 5.0-ml. samples were withdrawn at regular intervals and a slight correction was applied for the change of volume at that temperature. Evaporation was negligible.

The solvent mixtures were made up in the usual manner[18].

Rate Calculations:

The specific first order rate constants were determined graphically, by plotting 2.303 log. $a/(a - x)$ vs time expressed in seconds. (a is the initial ester concentration and x is the amount of ester hydrolyzed at the time t.)

Steric Results: Procedure

Two methods were used to determine the stereochemical path followed by the reaction; both involved measurement of the rotation of the alcohol after complete hydrolysis. It has already been explained at some length how difficult it is to separate the minute amount of 2-butanol involved in these experiments, from the mixture of water and dioxane. The three components boil at approximately the same temperature; the two aqueous azeotropes and the tertiary azeotrope also boil very close together. The first procedure(I) consisted in measuring the rotation of the final solution,

after that it had stood at the required temperature for a time sufficiently long to allow for at least 99 per cent hydrolysis. Together with this, an acidimetric titration and a determination of the amount of olefin formed permitted a fairly precise estimation of the amount of alcohol present in the solution. The actual rotations read however were so small, some as low as 0.05° in a 2 dm. tube, that the error involved varied between 5 and 20 per cent. In many cases, as many as twenty readings were taken. In each case, a blank solution, containing an equivalent amount of optically active 2-butanol, was treated under conditions absolutely identical to those of the ester and its initial and final optical rotations were determined. From a comparison of the values obtained in the actual experiment and in the blank, it was possible to obtain a value for the percentage of optical activity retained during hydrolysis.

The second method, (II), more reliable, consisted in the addition of a large amount of sodium carbonate until the solution, once neutralized and saturated, finally separated into two phases. The organic phase was then carefully dried in stages with potassium carbonate and distilled through a 25-cm. helicoidal-type column. A few drops of distillate came over in each case, between 86° and 98°. Their optical rotation was measured and always found quite small. From the measurement of their refractive indices, it was evident that they contained relatively large amounts of water. The next fraction of the distillate, b.p. 98°-98.5°,

usually about 2 ml. was then collected and its rotation carefully determined. Here again, the values actually observed were not very large; they represented however a decided improvement over method I, varying from 0.10° to 0.30° in a two dm. tube. The next fractions distilling over showed decreasing optical activity and were not recovered.

In order to determine the amount of 2-butanol in the recovered distillate, 1.0 ml. of L(-)-2-butanol, ($[\alpha]^{25}_D$ -13.05°) was dissolved in 25 ml. of 75 per cent aqueous dioxane (75% dioxane by weight) which was 0.25 N. in perchloric acid. The solution was neutralized with sodium carbonate and dried in stages with anhydrous potassium carbonate. Upon distillation through the same column as indicated above, two fractions were recovered; one, 1.5 ml. boiling between 98° and 98.5° and the second, 1.0 ml boiling between 98.5° and 99°. From their optical activities, α^{25}_D - 0.70° and α^{25}_D - 0.55° respectively, the concentrations of each solution was determined, and the values were plotted vs. their respective refractive indices. Another point of the plot was obtained by making a solution containing 0.40 g. of pure optically active alcohol in a 2.0-ml. dry dioxane solution. Finally the refractive index of a sample of freshly redistilled dioxane was measured. Table 1 summarizes all these data.

Table 1

RELATIONSHIP BETWEEN THE CONCENTRATION OF L (-)-2-BUTANOL IN ANHYDROUS DIOXANE AND THE REFRACTIVE INDEX OF THE SOLUTION

B.P.	$\alpha^{25}D$	% alcohol	$n^{25}D$
100° (745mm)	0	0	1.4193
98.5° - 99°	-0.55°	4.02	1.4178
98° - 98.5°	-0.70°	5.03	1.4174
---	-2.77°	20.6	1.4120

In each experiment the refractive index of the final distillate was measured and by comparison with a plot obtained from the above data, the concentration of alcohol was determined. A blank was always run simultaneously, like in procedure I, in order to determine the extent of spontaneous racemization of the alcohol under these conditions.

The rotations were measured whenever possible in 2 dm. semi-micro tubes but are always recorded for a 1 dm. length. The polarimeter was a Winkel-Zeiss instrument, with a water jacket at a constant temperature of 25.0°.

Olefin Determinations

The olefin analysis was done by the bromide-bromate method which has already been described in the first section of this thesis, in connection with the study of the hydrolysis of sec-butyl p-toluenesulfonate[19].

Rate of Racemization of L(-)sec-butyl Alcohol

The rate of racemization of optically active 2-butanol under the acidic conditions of the experiments described above was followed at 81° in water. The reaction was slow enough so as not to require any correction for the time needed to take a reading at 25°. A 20-ml. ampoule containing 10 ml. of the solution was removed at different intervals from the constant temperature bath and cooled in iced water until it reached room temperature. The ampoule was then opened and a 1.0-ml. sample withdrawn with a pipette. After being sealed the ampoule was replaced in the thermostat. A 1-dm. semi-micro polarimetric tube was used to measure the optical activities.

RESULTS

Kinetics

Acid Catalyzed Hydrolysis in Water - In aqueous solution, the acid hydrolysis followed a perfectly first order course and no substantial deviation was observed even after the reaction was 90 per cent over. Perchloric acid was used as catalyst and its concentration was only 2.4 times that of the sulfuric ester (0.1 mole per liter).

Since it was clear from previous work[4,7] as well as from evidence to be found in the next pages that the hydrolysis of alkyl hydrogen sulfates are acid catalyzed, no other concentration of perchloric acid was used.

The results are indicated in Table 2.

Acid Catalyzed Hydrolysis in Aqueous Dioxane - The rate of hydrolysis of sec-butyl hydrogen sulfate was followed at 81° in four different solvent mixtures of water and dioxane. These contained respectively 60, 70, 75 and 80 per cent dioxane by weight. In all the cases, the data fitted a first order curve perfectly.

As was to be expected, the rate increased with increasing amounts of dioxane in the medium and in 80 per cent aqueous dioxane the reaction was so rapid that it was necessary to reduce the temperature to 40° C. For the purpose of comparison, the rate of hydrolysis in 75 per cent aqueous dioxane was measured at both 40° and 81° C. and it was

Table 2

THE ACID CATALYZED HYDROLYSIS OF *sec*-BUTYL HYDROGEN SULFATE IN DIFFERENT SOLVENT MIXTURES

Solvent:	Temp. °C.	D[a]	$1/D$	$\frac{D-1}{2D+1}$	Ester M	Acid M	k_1 (sec^{-1})
Water	81	59.0	0.0170	0.488	0.1002	0.2320	1.22×10^{-5}
60% Diox.	81	17.5	0.0571	0.459	0.0995	0.2483	2.09×10^{-4}
70% Diox.	81	11.5	0.0870	0.438	0.0983	0.2470	9.30×10^{-4}
75% Diox.	81	9.25	0.108	0.423	0.0910	0.2462	1.92×10^{-3}
75% Diox.	40	13.7	0.0730	0.448	0.0910	0.2462	6.81×10^{-6}
80% Diox.	81	7.50	0.133	0.406	0.1[b]	0.25[b]	2.64×10^{-3}[b]
80% Diox.	46.0	10.9	0.0955	0.431_5	0.0961	0.2515	3.13×10^{-5}
80% Diox.	39.5	11.5	0.0870	0.438	0.0922	0.2513	1.0×10^{-5}

a) Dielectric constant at the temperature considered; data from ref. 20.

b) Calculated on the basis of the difference of rates between the same temperature in 75 per cent aqueous dioxane.

assumed that the logarithmic ratio of the first order rate constants could be used to obtain a value for the rate constant in 80 per cent aqueous dioxane at 81°.

All the data are presented in Table 2.

The results obtained in 75 per cent aqueous dioxane are shown in Tables 3 and 4 and plots of 2.303 log $\underline{a}/(\underline{a}-\underline{x})$ $\underline{vs}$ time for each reaction are presented in Figures 1 and 2. These are typical experiments.

The energy of activation ($\triangle E$) for the hydrolysis in 75 per cent aqueous dioxane was calculated from the Arrhenius expression:

$$\frac{d \ln. k}{dt} = \frac{\triangle E}{RT^2} \qquad \text{(eq. 1)}$$

which, on integration gives:

$$\log. (k_{T_2} / k_{T_1}) = \frac{\triangle E}{2.303\ R} \frac{T_2 - T_1}{T_2 T_1} \qquad \text{(eq. 2)}$$

if one can make the assumption that $\triangle E$ remains constant in the range of temperatures considered. This assumption was used here in spite of the fact that the change in temperature is quite large, since this cause of error is negligible in comparison with that introduced by the change of dielectric strength of the solvent.

Table 2 shows that, on passing from 40° to 81°, the dielectric constant of a medium containing 75 per cent dioxane and 25 per cent (weight) of water drops from 13.7 to 9.25.

It will be shown later how an equation can be obtained for the variation of the observed first order rate constant of hydrolysis of sec-butyl hydrogen sulfate with a change of dielectric constant, at a given temperature. For our present purpose, this equation can be written as follows:

$$\log \frac{k_{D2}}{k_{D1}} = \frac{10,850}{T_m}\left[\frac{D_2 - 1}{2D_2 + 1} - \frac{D_1 - 1}{2D_1 + 1}\right] + \frac{14,500}{T_m}\left[\frac{1}{D_2} - \frac{1}{D_1}\right]$$

(eq. 3)

This equation was used to determine what fraction of the rate increase, on passing from 40 to 81°, is due to the change of the dielectric strength of the solvent. For simplification, an average temperature of 60° was used in resolving the equation.

When this is done, a correcting fact of

$$\log (k_{D2}/k_{D1})_{T = 60} = 0.741$$

is obtained and if this is subtracted from the logarithmic ratio of the observed first order rate constants, equation 2 yields ΔE = 21,270 kcal per mole.

Another determination of the activation energy was attempted from the rates of hydrolysis of sec-butyl hydrogen sulfate in 80 per cent aqueous dioxane, at 39.5° and 46.0°. In this case, the change of temperature is certainly small enough to permit the approximation of a constant value of ΔE. The other cause of error, however, the change of

Tables 3 and 4

TYPICAL EXPERIMENTS

Rate of Acid Catalyzed Hydrolysis of sec-Butyl Hydrogen Sulfate in 75% aqueous Dioxane at 40.0° and 81.0°

Ester Conc.; 0.0910 mole/l. Perchloric acid conc.; 0.2462 n. standard sodium hydroxyde solution; 0.09970 n.

Time sec.	NaOH[a] ml.	$[H^+]$[b]	x[b,c]	$(a - x)$[b,d]	$\log a/(a-x)k_1 \times 10^{-6}$	
			40°			
0	12.35	0.2462	0.000	0.0910	0.00000	
1740	12.39	0.2470	0.0008	0.0902	0.00383	5.08
3600	12.55	0.2502	0.0040	0.0870	0.01952	12.45
10080	12.65	0.2522	0.0060	0.0850	0.02962	6.80
28000	13.20	0.2630	0.0168	0.0742	0.08864	7.22
73500	14.02	0.2796	0.0334	0.0576	0.19862	6.21
93000	14.60	0.2912	0.0450	0.0460	0.29628	7.45
						Av.:7.55
			81°			
0	12.35	0.2462	0.0000	0.0910	0.00000	
360	14.55	0.2901	0.0439	0.0471	0.28502	1820
600	15.55	0.3101	0.0639	0.0271	0.52607	2015
900	16.14	0.3218	0.0756	0.0154	0.77152	1970
1200	16.47	0.3284	0.0822	0.0088	0.01456	1945
1500	16.67	0.3324	0.0862	0.0048	1.27780	1960
						Av.:1942

a) per 5.0-ml. samples; b) concentration in mole/liter;
c) amount hydrolyzed; d) ester concentration.

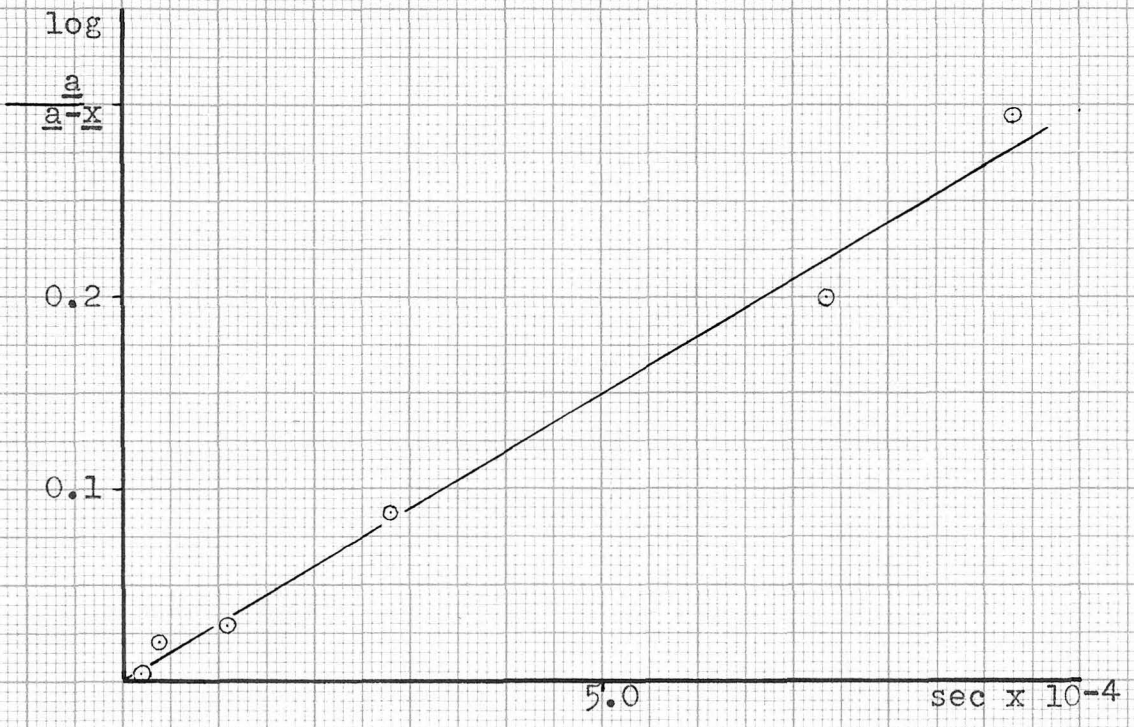


Fig. 1 - Rate of Acid Catalyzed Hydrolysis of sec-Butyl Hydrogen Sulfate in 75% Aqueous Dioxane at 40.0° (Table 3).

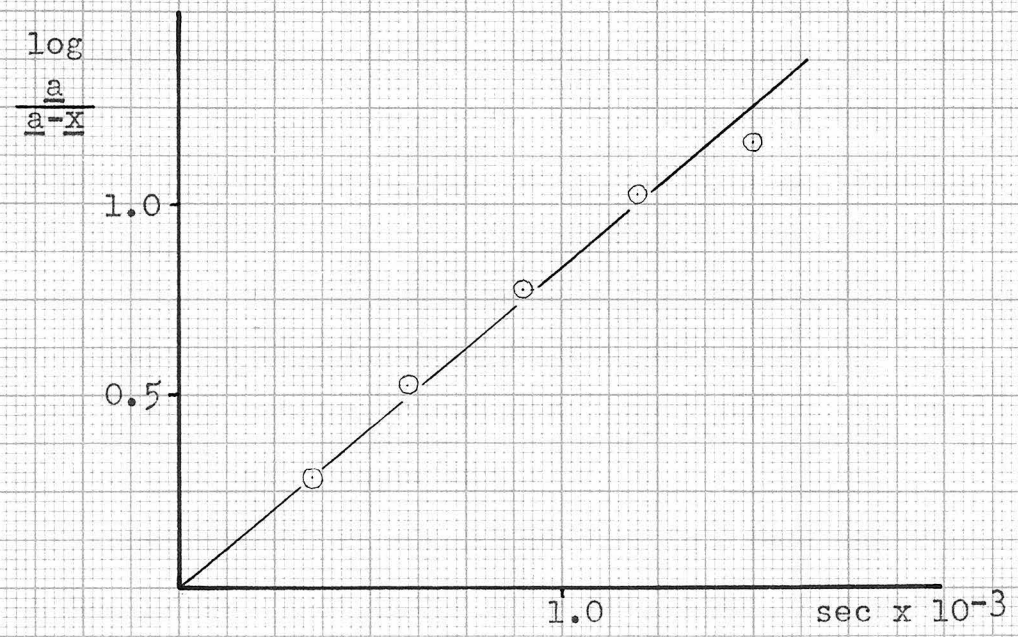


Fig. 2 - Rate of Acid Catalyzed Hydrolysis of sec-Butyl Hydrogen Sulfate in 75% Aqueous Dioxane at 81° (Table 4).

dielectric strength of the solvent is not much diminished. Indeed, Table 2 shows that with a rise from 39.5° to 46.0°, D drops from 11.6 to 10.9. The correcting factor here turns out to be log $(k_{D_2}/k_{D_1})_{T = 43} = 0.1233$ which leads to a value of the energy of activation of $\Delta E = 26{,}900$ kcal. per mole.

The discrepancy between these two values of the activation energy is understandable on the basis of the approximations made to obtain equation 3, which for example does not take into account the existence of specific solvent effects. The inaccuracy of the dielectric constant data, especially for low values of D, is also an important factor of error.

Racemization of Optically Active 2-Butanol - It was observed that L(-)-2-butanol racemizes slowly under the conditions of these kinetic experiments.

The rate of racemization was followed in water at 81° in the presence of 0.244 mole per liter of perchloric acid. The concentration of alcohol (0.304 mole per liter) was slightly higher than in the experiments with sec-butyl hydrogen sulfate since the rate had to be measured polarimetrically. Even so however, the readings were quite low and the accuracy was not any better than 5 per cent. Table 5 shows the results.

Table 5

RATE OF RACEMIZATION OF L(-)-2-BUTANOL IN DILUTE AQUEOUS SOLUTION OF PERCHLORIC ACID AT 81° C.

Time hrs.	α'	log α_o/α'	$k_1 \times 10^{-6}$ (sec^{-1})
0	-0.29	0	
46.0	-0.23	0.101	1.42 ± 0.45
139.5	-0.18	0.208	0.96 ± 0.17
175.0		0.280[a]	1.02 ± 0.16
211.5	-0.11	0.420	1.27 ± 0.15
259.0	-0.10	0.463	1.15 ± 0.13

Average value: $k_1 = (1.16 \pm 0.15) \times 10^{-6}$

Graphical determination: $k_1 = (1.12 \pm 0.15) \times 10^{-6}$

- -

a) value obtained from an independant experiment.

In the other solvent mixtures, the rate of racemization was not followed. Instead, a simple value of the change of optical activity was obtained from a "blank" experiment which was always run along with the hydrolysis of the alkyl sulfate under absolutely identical conditions. This procedure has already been described in detail in the experimental section.

The Elimination Reaction - The amounts of butylene formed during hydrolysis of sec-butyl hydrogen sulfate were measured in five cases. The proportion of olefin in the final product increases as expected, with increasing basicity of the solution, upon addition of dioxane.

The results obtained are indicated in Table 6.

Steric Results - Before describing these results, we want to again call attention to the rather large error involved in the methods used in measuring the optical activity. The data must be taken as a whole rather than separately and even so, they indicate only semi-quantitatively the importance of the solvent effect on the nature of the reaction. The methods have already been described in detail in the experimental section; let us add simply that in the first procedure (I), the correction for the amount of olefin formed during hydrolysis was calculated from the data in Table 6. For the amount of olefin formed in the blank, containing only optically active alcohol and the same acid concentration, the table gives only one figure, namely that for the reaction

Table 6

OLEFIN FORMATION DURING HYDROLYSIS OF sec-BUTYL HYDROGEN SULFATE AT 81°

Solvent	ester[a] M	butanol[a] M	$HClO_4$ [a] M	olefin %
Water	0.197	---	0.244	6.93
Water	0.00	0.304	0.244	5.15
60% Diox.	0.0995	---	0.249	3.8 ?
70% Diox.	0.0983	---	0.2470	10.1
75% Diox.	0.0910	---	0.2470	13.8

a) initial concentrations.

in water; in that solvent, the ratio of the amounts of butylene formed from the alcohol to that formed from the sec-butyl hydrogen sulfate is 74.5 per cent; it was assumed that it remains the same in the other solvent mixtures.

In order to be able to compare the final rotations of the 2-butanol in the hydrolysis and in the racemization or "blank" experiment, it is necessary to understand the kinetics of consecutive reactions. It is evident that the alcohol produced from the hydrolysis of the ester is racemized to a less extent than that left during the same time in the presence of the same acid concentration, in the blank run.

Let us consider the following system; where $\underline{k}_H$ and $\underline{k}_R$ represent the rates of hydrolysis of the ester and racemization of the alcohol respectively.

$$\underline{\underline{L}}\text{-}RSO_4H \xrightarrow{\underline{k}_H} \underline{\underline{L}}\text{-}ROH \xrightarrow{\underline{k}_R} \underline{\underline{DL}}\text{-}ROH$$

we have immediately:

$$-\frac{d(1-\underline{x})}{d\underline{t}} = \underline{k}_H (1-\underline{x}) \qquad \text{eq. 1}$$

and

$$\frac{d\underline{y}}{d\underline{t}} = \underline{k}_R (1-\underline{x}) \qquad \text{eq. 2}$$

This, on integration leads to:

$$(1 - \underline{x}) = e^{-\underline{k}_H \underline{t}} \qquad \text{eq. 3}$$

and

$$\underline{y} = \frac{\underline{k}_H}{\underline{k}_H - \underline{k}_R} (1 - e^{-\underline{k}_R \underline{t}}) - \frac{\underline{k}_R}{\underline{k}_H - \underline{k}_R} (1 - e^{-\underline{k}_H \underline{t}}) \qquad \text{eq. 4}$$

Here $\underline{x}$ is the fraction of $\underline{\underline{L}}$-$RSO_4H$ that has undergone hydrolysis and $\underline{y}$ is the fraction of $\underline{\underline{L}}$-$RSO_4H$ present as $\underline{\underline{DL}}$-ROH at time $\underline{t}$. Since we know from previous experiments that $\underline{k}_H$ is larger than $\underline{k}_R$, we shall be interested in the concentration of optically active alcohol, ($\underline{\underline{L}}$-ROH) at the time $\underline{t}_f$, corresponding to the substantial completion of the hydrolytic reaction.

At all times the concentration of $\underline{\underline{L}}$-alcohol is given by:

$$(\underline{\underline{L}}\text{-ROH}) = \underline{x} - \underline{y} \qquad \text{eq. 5}$$

at the time $\underline{t}_f$ however, $\underline{x}_f = 1$ and if $\underline{x}$ is replaced by 1 and $\underline{t}$ by $\underline{t}_f$ in equations 1, 2, 3 and 4 successively, the following expression results:

$$\underline{y}_f = 1 - \frac{\underline{k}_H}{\underline{k}_H - \underline{k}_R} e^{-\underline{k}_R \underline{t}_f} \qquad \text{eq. 6}$$

But on the other hand, from the measurement of the rate of racemization of $\underline{\underline{L}}$(-)-$\underline{sec}$-butyl alcohol, one knows that:

$$\frac{\alpha_o}{\alpha'_f} = e^{-\underline{k}_R \underline{t}_f} \qquad \text{eq. 7}$$

where α_o is the initial optical activity of the alcohol and α'_f its optical activity at the time $\underline{t}_f$. By substitution of eq. 7 into eq. 6 and then by replacement into eq. 5 noting again that $\underline{x}_f = 1$, one obtains finally:

$$(\underline{\underline{L}}\text{-ROH})_{\underline{t}_f} = \frac{\underline{k}_H}{\underline{k}_H - \underline{k}_R} \frac{\alpha' f}{\alpha_o} \qquad \text{eq. 8}$$

This expression represents the fraction of the total alcohol formed which has not been racemized at the end of the first step.

If α_f is now the optical activity observed at the end of the hydrolysis, at the time $\underline{t}_f$, the true rotation of the unracemized alcohol at that time is given by:

$$\frac{\alpha f}{(\underline{\underline{L}}\text{-ROH})} = \frac{\underline{k}_H - \underline{k}_R}{\underline{k}_H} \frac{\alpha_o \alpha_f}{\alpha' f} \qquad \text{eq. 9}$$

We then have the percentage of retention of optical activity during hydrolysis if the last expression is divided by the initial rotation α_o:

$$\% \text{ optical activity} = \frac{\underline{k}_H - \underline{k}_R}{\underline{k}_H} \frac{\alpha f}{\alpha' f} \qquad \text{eq. 10}$$

The respective values of $\underline{k}_H$ and $\underline{k}_R$ were obtained from previous experiments of from the blank test for racemization which afforded an inaccurate but sufficient value of $\alpha' f$.

The complete results and their interpretation by the use of equation 10 are described in Table 7. It might be interesting to note that the ratio α_f/α'_f remains constant after the time t_f; it is therefore not at all necessary to measure these rotations at that precise time. It is better however to do so since the rotations keep on decreasing and become more and more difficult to measure accurately.

Table 7

ACID CATALYZED HYDROLYSIS OF sec-BUTYL HYDROGEN SULFATE IN VARIOUS SOLVENTS AT 81° -- CONFIGURATIONAL RELATIONSHIP

Solvent:	Ester M	Acid[a] M	α_f[b]	α_f^7[d]		$\frac{k_H-k_R}{k_H}$	Opt. activity retained, % Uncorr.	Corr.[d]	Proc.[e]
Water	0.197	0.244	-1.48°	-7.0°	0.212	0.912	19.3	22.8	I
Water	0.0960	0.252	-1.72°	-10.2°	0.169	0.912	15.4	18.2	II
Water	0.0911	0.210[c]	-1.08°	-10.5°	0.103	0.912	9.4	11.0	II
60% Dioxane	0.100	0.249	-3.71°	-10.7	0.348	0.923	32.1	37.9	II
70% Dioxane	0.0964	0.247	(-0.09)[f]	(-0.13)[f]	0.69	0.928	64 ?	75 ?	I
75% Dioxane	0.0963	0.247	-6.73°	-11.4	0.591	0.930	55.0	64.3	II

- - - - - - - - - - - - - -

a) perchloric acid except in the third case. b) the rotation of L(-)-2-butanol ($[\alpha]^{25}D$ -13.25°) in anhydrous dioxane is $[\alpha]^{25}D$ -13.85. c) sulfuric acid was used instead of perchloric acid; in this case, the hydrogen ion concentration is approximately 0.22 normal. d) corrected for the fact that the alkyl sulfate was only 85.5 per cent optically pure. e) procedure I and II are described in detail in the experimental section, page 82. f) these values are the observed rotations rather than the specific rotations which could not be determined.

DISCUSSION

Inspection of the results described in the preceding pages will reveal an extraordinary large increase of the rate of hydrolysis of sec-butyl hydrogen sulfate when the ionizing power of the solvent is decreased. On passing from water to 80 per cent aqueous dioxane, the first order specific rate constant is increased by a factor of 216.

This effect is in complete agreement with the assumption already proposed that the free acid sulfate molecule is actually the reacting species undergoing hydrolysis. In water, the equilibrium

$$H_3O^+ + R\text{-}OSO_3^- \rightleftharpoons H_2O + R\text{-}OSO_3H \qquad \text{eq. 1}$$

lies far over to the left and very few acid molecules are present in the solution. When successive amounts of dioxane are added to the water, the dissociation constant of the alkyl sulfuric ester is considerably decreased while that of the perchloric acid used as catalyst is not much influenced. Since the rate is proportional to the concentration of acid molecules, a large acceleration is observed.

$$R\text{-}OSO_3H + H_2O \longrightarrow R\text{-}OH + {}^-OSO_3H + H^+ \qquad \text{eq. 2}$$

This important effect of the solvent is unfortunately of a complicated nature because two reaction steps at least are involved in the overall hydrolysis. A differentiation is possible however since the two steps, represented by

equations (1) and (2) constitute two entirely different reactions, which are influenced by a change of solvent in completely opposite ways.

If $\underline{k}_1$ is the observed first order rate constant, $\underline{k}_H$ the true rate constant of hydrolysis and $\underline{K}_a$, the acid dissociation constant of sec-butyl hydrogen sulfate (or any other alkyl hydrogen sulfate), the following relation between these three entities can be easily obtained:

$$\underline{k}_1 = \frac{\underline{k}_H}{\underline{K}_a} \cdot \frac{\underline{f}_{H^+} \underline{f}_{RSO_4^-}}{\underline{f}_{RSO_4H}} \qquad \text{eq. 3}$$

in which the $\underline{f}$'s represent the respective activity coefficient of the various ions and molecules involved in the first reaction step.

From equation 3 it is possible to derive an expression for the variation of log $\underline{k}_1$ with the change of dielectric strength of the solvent.

The Scatchard formula (21) for the variation of the rate of interaction between two ions in a solvent of dielectric constant $\underline{D}$, with the change of the dielectric constant, can be considerably simplified if one works in sufficiently dilute solutions so that the ionic strength term can be neglected. We shall assume that this assumption is justified in our case and we shall write the Scatchard expression under the form[22]:

$$\ln \frac{f_{H^+} f_{RSO_4^-}}{f_{RSO_4H}} = \frac{\varepsilon^2}{kT}\left[\frac{1}{D} - 1\right]\frac{z_{H^+} z_{RSO_4^-}}{r} \qquad \text{eq. 4}$$

in which ε is the charge of the electron, k the Boltzmann constant, the z's are the respective charges of each ion and r is the distance to which two ions must approach in order to react.

If now we replace the activity coefficient term in equation 3 by its value from equation 4, we obtain the following expression:

$$\log \underset{\chi=o}{k_1} = \log \underset{\chi=o}{k_H} + pK_a - \frac{z_{H^+} z_{RSO_4^-} \varepsilon^2}{kT\, r \times 2.303}\left[\frac{1}{D} - 1\right] \qquad \text{eq. 5}$$

valid only at zero ionic strength one sees; that a plot of log k against D^{-1} should yield a straight line.

When such a plot is made, using our experimental data (Table 7), a line is obtained which is almost straight for low values of D^{-1} but has a rather pronounced curvature about $D^{-1} = 0.05$ i.e. for values of the dielectric constant lower than 20 (I, Fig. 3).

This deviation from a straight line for solvents of poor dielectric strength could be explained as a consequence of some abnormal solvent effect. If, for example, a large number of water molecules accumulate around the relatively polar alkyl sulfate, a center of higher dielectric strength will be created and the observed rate will be lower than

expected. It is indeed quite possible that the decreasing solubility of the alkyl sulfate upon the addition of dioxane to the medium causes the water molecules to accumulate around it.

Although we recognize the possibility of abnormal solvent effects, we shall nevertheless try to determine to what extent the curvature observed in the plot of log $\underline{k}_1$ vs $\underline{D}^{-1}$ is due to a change in the value of log $\underline{k}_H$, (true rate constant) a change which was neglected in plotting equation 5.

Since we are now dealing with a reaction between a dipolar molecule ($R\text{-}OSO_3H$) and the solvent, we can apply to it the Laidler-Eyring treatment[23]. If the reaction under consideration has for the rate determining step an S_N1 ionization:

$$R\text{-}OSO_3H \underset{}{\overset{\underline{k}_H}{\rightleftharpoons}} R^+ + HSO_4^- \qquad \text{eq. 6}$$

$$R^+ + H_2O \xrightarrow{\text{fast}} R\text{-}OH + H^+ \qquad \text{eq. 7}$$

then, the Laidler-Eyring expression, at zero ionic strength, takes the following form:

$$\log \underset{\chi=o}{\underline{k}_H} = \log \underset{\substack{\chi=o \\ \underline{D}=1}}{\underline{k}_H} - \frac{1}{\underline{kT}} \frac{\underline{D}-1}{2\underline{D}+1} \left[\frac{\underline{M}^2_{RSO_{4H}}}{r^3_{RSO_{4H}}} - \frac{\underline{M}^2_T}{r^3_T} \right] + \Phi \qquad \text{eq. 8}$$

in which log $\underline{k}_H$ represents the specific first order rate constant of the reaction in the standard state of reference, here the vacuum, where the ionic strength is zero and the dielectric constant unity: the $\underline{M}$'s and the $\underline{r}$'s are respectively

the dipole moment and the radii of the alkyl hydrogen sulfate and of the transition state(T). Φ indicates the possibility of specific solvent effects (non electrostatic).

Since the term in $\underline{M}$'s and $\underline{r}$'s cannot be calculated, we shall rewrite equation 8 under the simpler form of equation 9.

$$\log \underset{\chi=0}{\underline{k}_H} = \log \underset{\substack{\chi=0 \\ D=1}}{\underline{k}_H} + \frac{\underline{B}_1}{T} \frac{\underline{D} - 1}{2\underline{D} + 1} + \Phi \qquad \text{eq. 9}$$

with:

$$\underline{B}_1 = -\frac{1}{\underline{k}} \left[\frac{\underline{M}^2_{RSO_4H}}{\underline{r}^3_{RSO_4H}} - \frac{\underline{M}^2_T}{\underline{r}^3_T} \right] \qquad \text{eq. 10}$$

Similarly, if the hydrolysis follows a bimolecular, S_N2 displacement, whether on the carbon atom or on the sulfur atom, the Laidler-Eyring expression will assume the form:

$$\log \underline{k}_H = \log \underline{k}_H + \frac{\underline{B}_2}{T} \frac{\underline{D} - 1}{2\underline{D} + 1} + \Phi \qquad \text{eq. 11}$$

with

$$B_2 = -\frac{1}{\underline{k}} \left[\frac{\underline{M}^2_{RSO_4H}}{\underline{r}^3_{RSO_4H}} + \frac{\underline{M}^2_{H_2O}}{\underline{M}^3_{H_2O}} - \frac{\underline{M}^2_T}{\underline{r}^3_T} \right] \qquad \text{eq. 12}$$

A direct consequence of these formulas is that a plot of $\log \underline{k}_H$ $\underline{vs}$ $(\underline{D}-1)/(2\underline{D}+1)$ should yield a straight line, the

slope of which depends on the nature of the mechanism prevailing. These slopes are positive in both cases and obviously $\underline{B}_1$ is larger than $\underline{B}_2$.

In order to test this theory, the initial slope of curve I in Figure 3 was determined by graphical differentiation. A plot of $\triangle \log \underline{k}_H / \triangle \underline{D}^{-1}$ against $\underline{D}^{-1}$ (curve II) afforded a relatively good straight line and, by extrapolation to $\underline{D}^{-1} = 0$ yielded the initial slope (42.0, Table 8). It is quite difficult to determine exactly where a straight line, having this initial slope, should join the actually observed curve I. This fortunately is unimportant since we are only interested in the increase of the deviation from the theoretical straight line at any point along curve I. It seems reasonable to make the straight line tangent to curve I at $\underline{D}^{-1} = 0$; this was done and is indicated by curve III (Figure 3).

The next step was the measurement of the difference of log $\underline{k}_H$ values ($\triangle' \log \underline{k}_H$) from curves III and I for a given value of $\underline{D}^{-1}$. These differences are indicated in Table 8, together with the data used in the establishment of curves I, II and III.

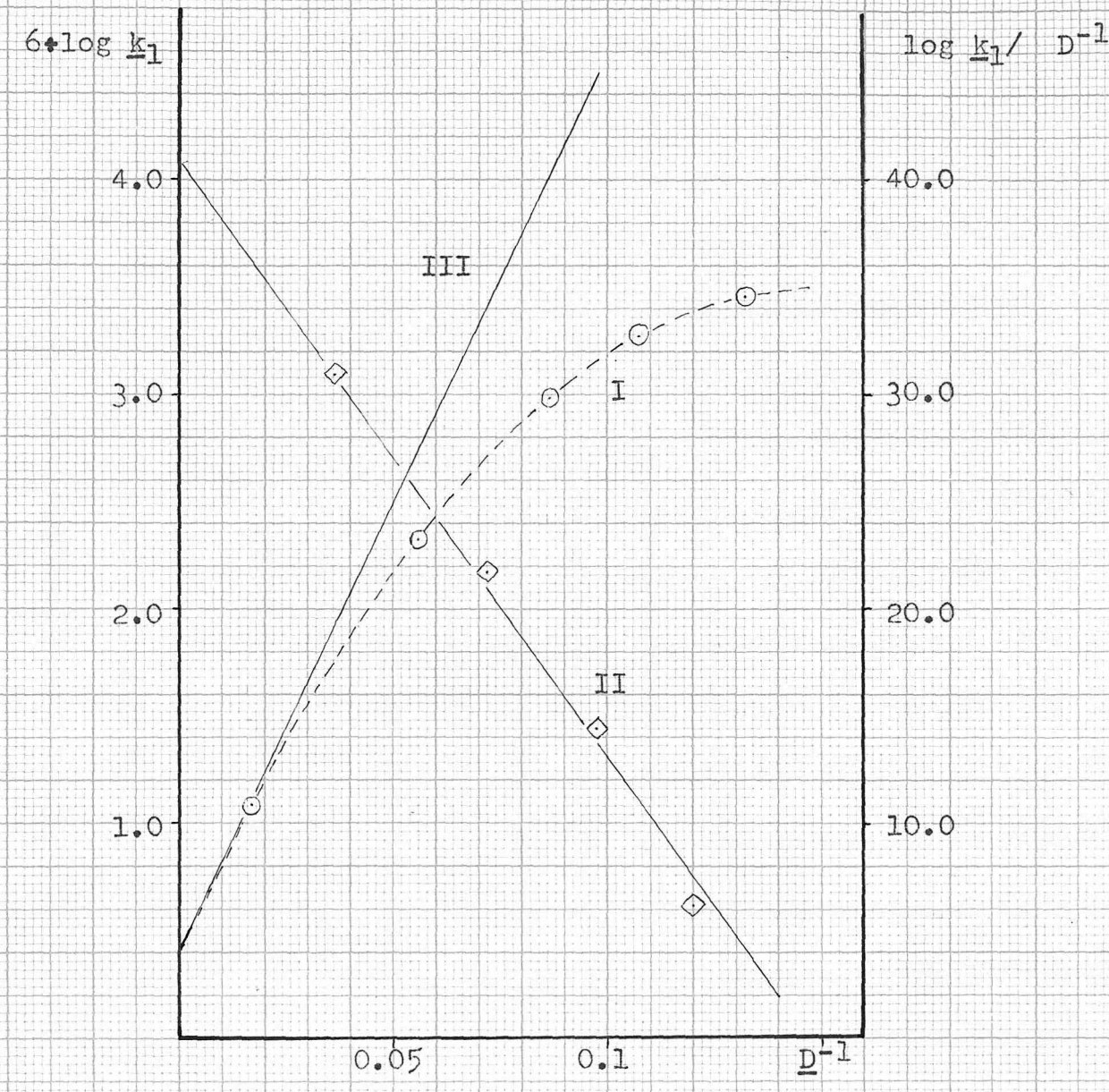


Fig. 3 - Calculation of the Variation of log $\underline{k}_H$ with a Change of the Dielectric Constant of the Solvent.

TABLE 8

CALCULATION OF THE VARIATION OF LOG k_H WITH A CHANGE OF THE DIELECTRIC CONSTANT OF THE SOLVENT AT 81°

Solvent	D	D^{-1}	$\frac{D-1}{2D+1}$	$\log k_1$[a] + 6.0	$\frac{\Delta \log k_1}{\Delta D^{-1}}$[b]	$\Delta' \log k_H$[c]
Water	59.0	0.0170	0.488	1.0864		0.026
		0.0375			30.77	
60% Diox	17.5	0.0571	0.459	2.3202		0.415
		0.0715			21.68	
70% Diox	11.5	0.0870	0.438	2.9685		0.990
		0.0975			14.22	
75% Diox	9.25	0.108	0.423	3.2672		1.560
		0.1205			6.18	
80% Diox	7.50	0.133	0.406	3.4216		2.025
		0.000			42.0	

a) Curve I; b) Curve II; c) Curve III

When a plot is made of Δ'log k_H *vs* (D-1)/(2D+1), a straight line is obtained for all the low values of D; the last point however, corresponding to the reaction in water, does not line up with the others and the deviation is certainly larger than the experimental error (curve IV)(Fig. 4).

The interpretation of this curve is of course dependent first of all upon the acceptance of the theories of Laidler and Eyring[22] which are, themselves based on the work of Kirkwood[23]. Their mathematical treatment has been tested many times[24] and we shall therefore accept them as reasonably exact.

We have seen that on the basis of these theories, a profound change in the nature of the mechanism of hydrolysis under study should be recognizable at a curvature in the plot of log k_H *vs* D-1/2D+1. The curvature observed in Figure 4 however, is completely different from the one we obtained in the case of the hydrolysis of *sec*-butyl-*p*-toluenesulfonate, namely, the slope (B/T) decreases when the dielectric constant of the solvent is increased.

The value of the B term for the straight portion of curve IV is 10,600 which, if one refers to the table shown on page 6 , agrees fairly well with the corresponding values of B for secondary alkyl halides in ethanol-water mixtures and for *sec*-butyl-*p*-toluenesulfonate in dioxane-water mixtures of low water content.

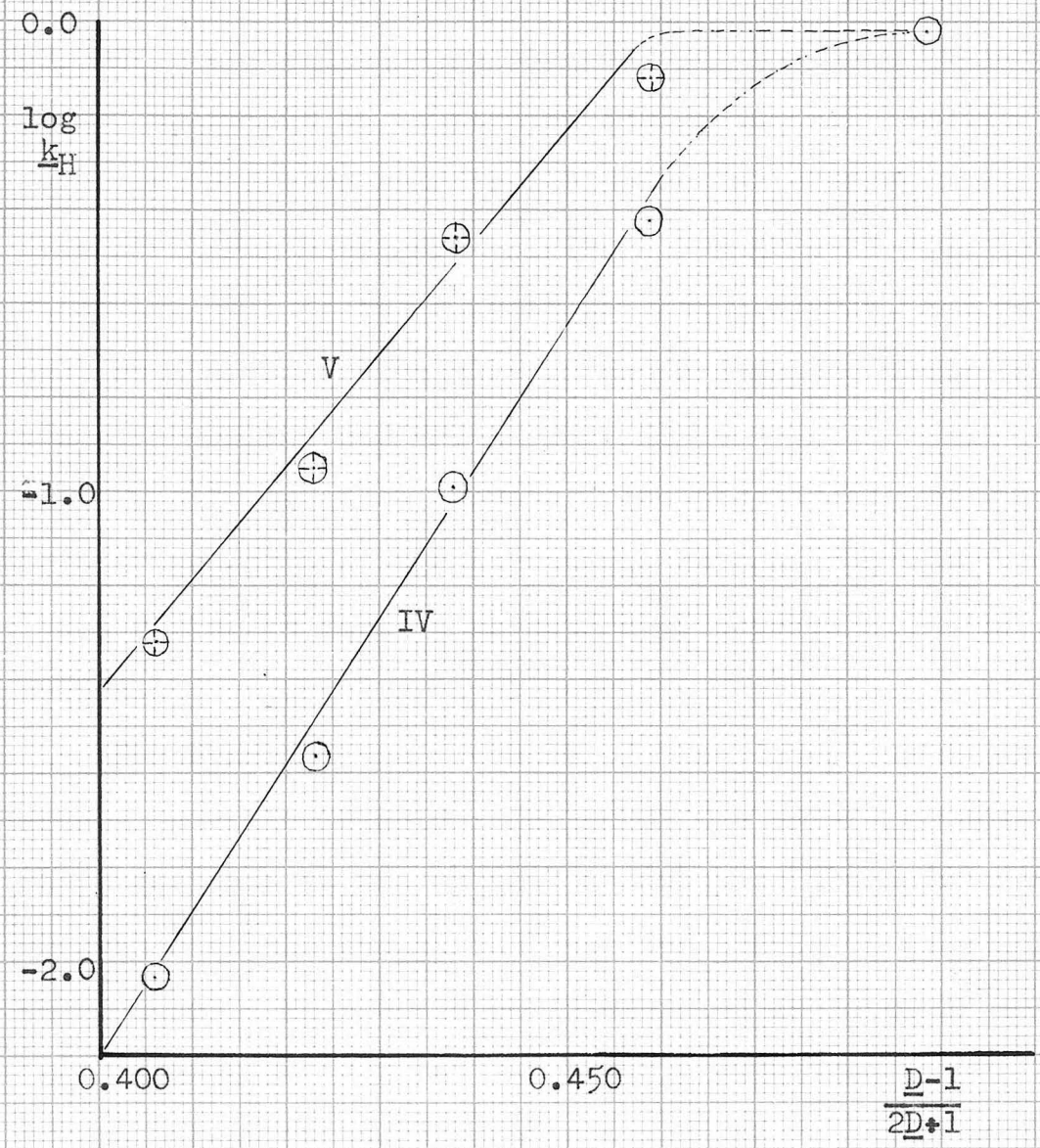


Fig. 4 - Variation of the True Rate of Hydrolysis of sec-Butyl Hydrogen Sulfate with $(D-1)/(2D+1)$. ⊕ Taking account of the water concentration. ⊙ Not taking account of the water concentration.

It seems therefore quite safe to disregard a purely ionic mechanism, analogous to that postulated for the hydrolysis of tertiary alkyl halides (B-term of the order of 50,000). Instead, and on the basis of the solvent effect alone, one might be tempted to assign to this reaction of sec-butyl hydrogen sulfate a bimolecular course similar to that involved in the hydrolysis of the primary and of some secondary halides in ordinary solvent mixtures, and dependent both on the solvolytic effect and on the nucleophilic character of the medium.

If this were true, however, one should observe a change of configuration of the asymmetric carbon atom upon hydrolysis while, in fact, a retention of configuration is recorded.

Furthermore, the presence of bisulfate ions in an aqueous perchloric acid solution of the ester produces a sharp decrease in the optical activity of the 2-butanol recovered at the end of the reaction (Table 7, page 102, third case). This could be interpreted in favor of an ionic mechanism[25], but can also be explained on the basis of a bimolecular hydrolysis in which the reacting solvent molecule is momentarily replaced by a more nucleophilic bisulfate ion with the resulting formation of an inverted sec-butyl hydrogen sulfate molecule. The last reaction must occur between the bisulfate ion and the alkyl sulfate molecule or at the most, with its transition state, because optically active 2-butanol is not racemized any faster in

the presence of bisulfate ions in an acid solution.

All this leads us to the conclusion that we are here confronted with a complex bimolecular mechanism, involving probably displacement on both the asymmetric carbon atom and the sulfur atom.

If this is so, then curve IV in Figure 4 should be recalculated for the change in the concentration of water since this solvent is now stoechiometrically involved in the reaction. The data are given in Table 9 and the recalculated curve V is shown in Figure 4.

Table 9

RECALCULATION OF k_H TAKING ACCOUNT OF THE WATER CONCENTRATION

Solvent	Wt % H_2O	m/l(H_2O)	log H_2O	log k_H	log k'_H[a]
Water	100	55.5	0.0000	0.026	0.026
60% Diox.	40	21.8	0.3019	0.415	0.113
70% Diox.	30	16.3	0.5282	0.990	0.462
75% Diox.	25	13.6	0.6069	1.560	0.953
80% Diox.	20	10.83	0.7040	2.025	1.321

a) recalculated values of the first order rate constant

The net result of this recalculation is to accentuate the curvature between the two upper points. Whether this

curvature has any real meaning is questionable on different grounds. First, it is dependent upon the choice of the slope of the straight line III in Figure 3, and although that slope was obtained by an extrapolation, this procedure may not be permissible. If for example the initial slope is arbitrarly chosen as twice its indicated value, the five points of Figure 4 lie on a straight line without any noticeable curvature between the two upper ones. Secondly, it is not certain that the continuity of electrostatic effects, when passing from pure water to mixtures of dioxane and water, can be safely assumed. This would not be too surprising in view of the evidence recently[26] furnished that dioxane is capable of forming an addition complex with hydrochloric acid in water-dioxane.

We shall therefore not pay too much attention to that abnormal behavior between 60 per cent aqueous dioxane and water and consider only the straight part of curve IV, which indicates an excellent agreement of our experimental data with the theories of Laidler and Eyring.

For the straight part of the curve we can write now the complete empirical equation describing the variation of the observed first order rate constant of hydrolysis of sec-butyl hydrogen sulfate with the dielectric constant of the solvent:

$$\log \frac{k_{D2}}{k_{D1}} = \frac{10,850}{T_m} \left[\frac{D_2 - 1}{2D_2 + 1} - \frac{D_1 - 1}{2D_1 + 1} \right] + \frac{14,500}{T_m} \left[\frac{1}{D_2} - \frac{1}{D_1} \right]$$

Eq. 13

Equation 13, which has already been used, page 90, to obtain a correcting factor for the determination of the activation energy, contains, therefore, two terms, one corresponding to the change of the acid constant of sec-butyl hydrogen sulfate with a change of solvent and the other representing the actual change of the rate of hydrolysis with the same change of solvent.

From all this, we can draw the following conclusions:

a) On the basis of the solvent effect, a unimolecular ionic mechanism is extremely improbable.

b) On the basis of the bisulfate ion effect on the extent of racemization, both S_N1 and S_N2 mechanisms could operate.

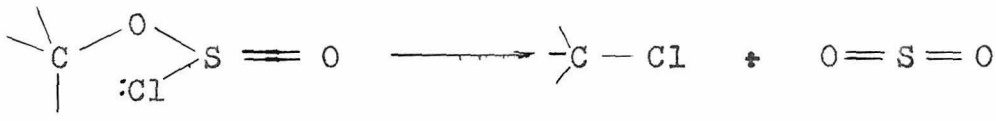
c) On the basis of the changes in configuration, some sort of internal displacement mechanism, possibly involving the attack of a water molecule on the sulfur atom, must be postulated together with an S_N1 or an S_N2.

If one accepts the solvent effect as sufficiently reliable, the first of these conclusions eliminates completely the simple ionic or S_N1 process and one is left with a combination of two nucleophilic displacement reactions, one on the carbon atom, accompanied by inversion of configuration, and the other on the sulfur atom, accompanied by an internal rearrangement and retention of configuration.

Since however the application of the Laidler-Eyring treatment gives a straight line, when log k_H is plotted vs $(D-1)/(2D+1)$, it is probably more exact to say that we are

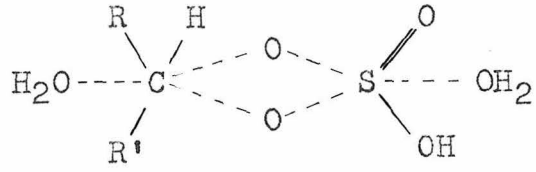
confronted with a <u>single</u> mechanism, intermediate between the two others or, more exactly, a hybrid of these two.

Hughes, Ingold and their collaborators[27,28] have already postulated the existence of such an internal displacement mechanism on carbon (S_Ni), to explain the almost complete retention of configuration during chlorination of phenylalkylcarbinol with thionyl chloride in the absence of pyridine. Their main evidence however, like ours, is the fact that configuration <u>is</u> retained during the replacement[29]. They picture the S_Ni mechanism as a simple "four center" rearrangement taking place as follows:

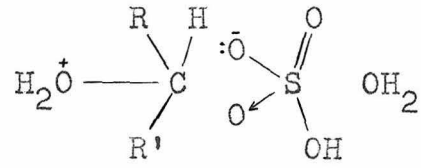


In the present case, we believe that a similar rearrangement of the alkyl hydrogen sulfate molecule takes place, initiated by a combination of nucleophilic and solvolytic attack from the medium.

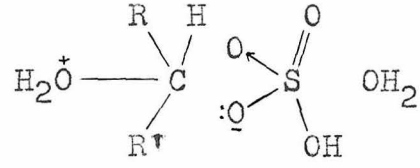
If we keep in mind that we can only consider a single mechanism, we arrive at the following picture for the transition state:



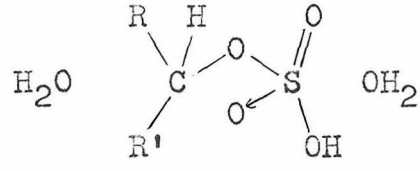
which is actually the combination of the six resonating structures:



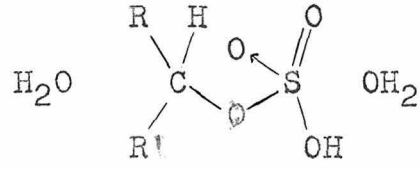
I



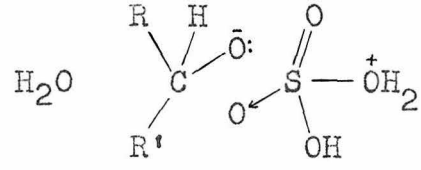
II



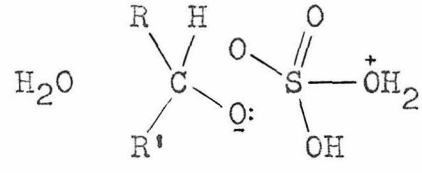
III



IV



V



VI

We have purposedly neglected to indicate the presence of protons in the transition state in order to show better the double dipolar nature of this complex which results from the interaction of three dipolar molecules. Actually, the negative charges are neutralized by the hydrogen ions surrounding them but this is also true for the three reacting dipoles and the case can still be treated as if free dipolar entities were involved.

In a strongly ionizing solvent, the sulfate group shows little affinity for protons, but the ionization of the alkyl-oxygen bond is facilitated. In other words, the center of low electron density is unequally distributed between the carbon and sulfur atoms, being mostly localized on the former. Structures I and II contribute extensively to the transition state and a large proportion of the hydrolysis proceeds with inversion of configuration.

In a weakly ionizing solvent like aqueous dioxane, the proton affinity of the sulfate group is considerably increased while ionization of the alkyl-oxygen bond is much less likely than in water. Structures V and VI predominate and retention of configuration is observed.

In both cases the transition complex remains essentially the same; the only difference is a gradual shift of the center of low electron density from carbon to sulfur. It is important to note that if no ionization of the alkyl-oxygen linkage is possible at all, a likely occurrence for example

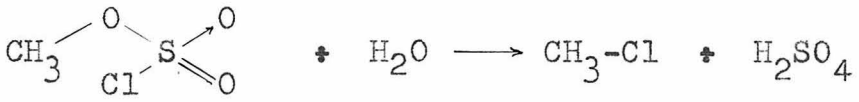
in the case of a primary alkyl hydrogen sulfate, no such transition state can exist. Displacement then can only take place on the sulfur atom and the configuration is completely retained. We have seen that this must be the case for neopentyl hydrogen sulfate. For the tertiary alkyl derivatives, on the contrary, ionization of the carbon-oxygen bond is too extensive for the rearrangement to take place and racemization must be the general rule.

The base catalyzed hydrolysis of sec-butyl and other alkyl hydrogen sulfate can also be explained on the basis of this mechanism. An attack on the sulfur atom is quite unlikely under these conditions however because of the negative charge on the sulfate group. When a dialkyl or cyclic sulfate is considered instead, the rearrangement mechanism can operate again and indeed retention of configuration was observed when the sulfate ring of 2,3-butanediol was opened under basic conditions. The same compound, under acidic or neutral conditions is hydrolyzed with inversion of configuration probably because its sulfur atom is not sufficiently electro positive to attract a weakly nucleophilic water molecule.

A similar observation was made with phosphate esters[30]. Detailed studies with O_{18}-rich water have shown that in the alkaline hydrolysis of trialkylphosphates, the usually expected -OR displacement occurs while in the acidic or "water" hydrolysis, a rupture of the alkyl-oxygen link takes place, at least in the first step.

A certain number of facts can be found in the literature which more or less support the hypothesis of an internal displacement mechanism for the esters of sulfuric and phosphoric acid and for their haloderivatives.

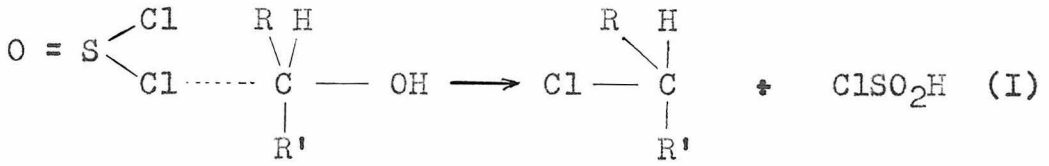
It has been found for example[31], that the reaction of methylchlorosulfonate with water in the presence of methanol yields methyl chloride in proportions increasing with the amount of methanol.



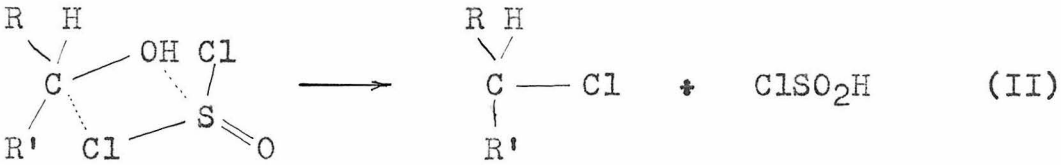
A similar result was observed for ethylchlorosulfonate[32] which, with concentrated potassium hydroxyde in water or alcohol yields ethyl chloride. One might point out that in this case, no negative charge can prevent a hydroxyl ion or a water molecule from reaching the sulfur atom.

Gerrard, in an extensive series of papers[33-39], has provided an elegant explanation for the different reactions involved in the replacement of a hydroxyl group by a halogen atom with thionyl halides, phosphorus trihalides, oxyhalides, etc... Among other things he has demonstrated the importance of the presence of a tertiary base like pyridine in these reactions. We have seen for example that methylphenylcarbinol reacts with thionyl chloride in the absence of pyridine to yield the chloride with retention of configuration. Gerrard pictures this as being one of the three possible reactions which can occur under these conditions, namely, an "end-on" attack of thionyl chloride on

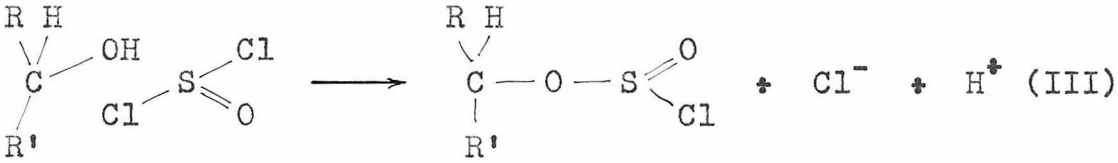
the α-carbon atom, with inversion of configuration (I); a "broadside attack" followed by rearrangement and dissociation, with retention of configuration (II) and finally, the formation of chlorosulfinic esters which remain as such, (III) thus:



(I)



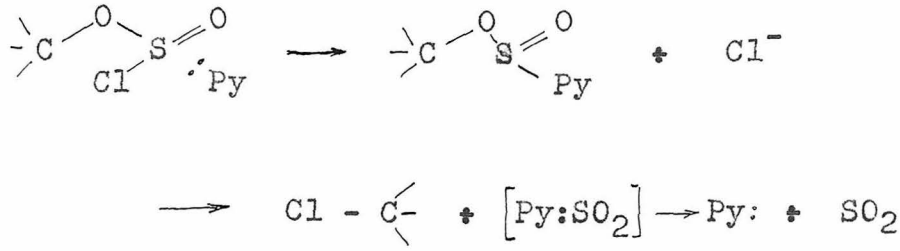
(II)



(III)

When pyridine is present, it not only facilitates the inversion mechanism (I) but also catalyzes the decomposition of the chlorosulfinate into the chloride by a mechanism fairly similar to that pictured by us for the hydrolysis of sec-butyl hydrogen sulfate. The main difference is due to the fact that pyridine, although a rather poor solvent possess a high nucleophilic character. No ionization of the alkyl-oxygen bond occurs and the molecule does not go

through a rearrangement, instead, a chloride ion is displaced and attacks the back side of the α-carbon atom.

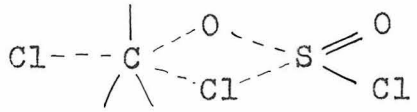


The case of the phosphorous compounds is quite similar with the distinction that pyridine is unable to catalyze the decomposition of the chlorophosphites. The phosphoric and sulfuric derivatives also behave similarly and their halo-esters are all catalytically decomposed by tertiary bases. Inversion of configuration is the general rule.

From a careful study of these reactions, Gerrard comes to the conclusion that in the absence of pyridine, the halo-esters are not intermediates in the formation of alkyl halides from alcohols. The rather large variations in the optical activity of the halide when different reagents are used is explained on the basis of the different contributions of the various mechanisms described before.

Gerrard's "broadside approach" is not essentially different from the mechanism that we have proposed for the hydrolysis of secondary alkyl hydrogen sulfates especially if one considers the extreme difference of conditions involved in each reaction. Indeed a possible transition state for the reaction between an alcohol and thionyl chloride

can be pictured, thus:



very similar to the one indicated on page 108, for the hydrolytic reaction.

Since primary alcohols are not available optically active, it is difficult to determine which of Gerrard's mechanisms apply to their halogenation. The results mentioned earlier which were obtained with methyl and ethyl chlorosulfonates are insufficiently specific since it is not clear whether the displacement of the chloride ion from the sulfur atom and its reaction with the α-carbon atom, are two consecutive or simultaneous reactions.

Gerrard and his coworkers[40] however, repeating the experiments of Whitmore and Rothrock[41] have recently shown that neopentyl alcohol reacts readily with thionyl chloride to yield a chlorosulfinate which shows reluctance to decompose even at 110°, in the presence of pyridine hydrochloride. The same thing is true of the reaction with phosphorus trichloride, the phosphite being isolated, instead of reacting with a chloride ion as in the reactions of 1-butanol and 2-octanol. In view of these facts, one must come to the conclusion that the "broadside approach" mechanism with formation of a halide of configuration identical with that of the alcohol does not work for primary compounds. If the identification of Gerrard's mechanism with ours is

possible therefore, we have here some evidence that internal rearrangement can only occur when the polarization of the alkyl-oxygen bond is sufficient (sec and tert-derivatives).

Another interesting example which might be related to our observations is provided by the reactions of optically active sec-octylchloroformate. When this compound is heated for some hours, decomposition into (-)-octyl chloride occurs[42] but when it is warmed up in the presence of pyridine, the (±)-halide is recovered[43]. Here again we seem to have the indication that pyridine is too powerful a nucleophilic reagent to permit the rearrangement to take place, and the same conclusion comes out of the recent work of Clark and Todd[44] who showed that bases like pyridine are not only capable of reacting at the sulfur atom of a chlorosulfite, for example, and to displace a chloride ion from it, but can also attack the back side of the α-carbon atom and become alkylated. The tertiary alkyl esters possess a carbon-oxygen bond so highly polarized or even ionized that rearrangement is probably impossible under any conditions and racemization with an excess of inversion must occur.

Table 10

INFLUENCE OF THE SOLVENT ON THE STERIC RESULT IN THE SOLVOLYSIS OF sec-ALKYL HYDROGENSULFATES AND SIMILAR ESTERS

Solvent	Nucleoph. character	Dielectric strength	C-O bond polarization	Mechanism	Steric Result
Water	high	high	large	S_N1	Racemization and Inversion
Pyridine	high	low	small	S_N2 on S and on C	Inversion
Aq.Dioxane	low	low	small	S_Ni	Retention

For the secondary alkyl sulfate (intermediates as usual), the effects that we observed by measuring the dielectric constant and the nucleophilic character of the solvent can be fairly well explained on the same basis as Gerrard's results and furnish a strong support in favor of the hypothesis of a double displacement mechanism. In Table 10 we have summarized what we believe must be the solvent effect on the hydrolysis of alkyl hydrogen sulfates, chlorosulfonates and probably phosphates for which the "double displacement" mechanism (actually a combination of S_N1, S_N2 and S_Ni) can be postulated.

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IV. THE HYDROLYSIS OF L(-)-sec-BUTYL NITRATE

THE HYDROLYSIS OF sec-BUTYL NITRATE

We have just seen that the hydrolysis of L(-)-sec-butyl hydrogen sulfate under acid conditions takes place with retention of configuration. In opposition to this, however, the hydrolyses of cyclic sulfates[1] and that of trialkyl phosphates[2] are not acid catalyzed and lead to more or less complete inversion of configuration.

This apparent contradiction is not an isolated case and it appears to be a fairly general rule that the neutral or, as it is sometimes called, the "water" hydrolysis, occurs with opening of the alkyl-oxygen bond. To illustrate this point, a few examples are summarized in Table 1 in which is clearly indicated the general relationship existing between the conditions of hydrolysis, acidic, neutral or basic, and the steric course of the reaction.

Two noticeable exceptions are immediately evident; the first is the occurrence of a Walden inversion during alkaline hydrolysis of alkyl hydrogen sulfates. This is quite understandable if one recalls that these compounds bear a negative charge in a basic solution which makes a frontal attack on the sulfur atom extremely difficult. The second important deviation from the general rule is furnished by alkyl p-toluenesulfonates and similar esters. No simple explanation is available here but it is not improbable that the benzene ring is responsible for this exceptional behavior.

Table 1

THE STEREOCHEMISTRY OF SOME HYDROLYTIC REACTIONS

Ester:	Acid hydrol.	Neutral hydrol.	Basic hydrol.
Carboxylic	Retention	Racemization[a]?	Retention[a,b]
Lactones	Retention	Inversion	Retention[c]
Acid sulfates	Retention	Inversion	Inversion[d,e]
Neutral sulfates	not catal.	Inversion	Retention[d]
Neutral phosph.	not catal.	Inversion	Retention[f]
Tosylates	not catal.	Inversion	Inversion[d,g,h]

a) Kenyon, Partridge and Phillips, J. Chem. Soc., 85 (1936) b) Hammett, "Physical Organic Chemistry", McGraw Hill Co., New York, 1940, p. 358; also, Kenyon and Phillips, J. Chem. Soc., 1936 to 1942. c) Olson and Miller, J. Am. Chem. Soc., 60, 2687 (1938). d) This thesis, pages 35, 72 and 1. e) Burwell, see ref. page 127. f) Ref. 2. g) Phillips, J. Chem. Soc., 44 (1923). h) Ref. 10.

If one accepts the idea that retention of configuration in the hydrolysis of sulfuric, phosphoric or carboxylic esters is due to a nucleophilic displacement on sulfur, phosphorus or carboxylic carbon, respectively, one comes to the conclusion that a water molecule is only able to attack these central atoms when a mechanism of acid catalysis operates.

In order to see whether this conclusion is also valid for esters other than those mentioned above, we have investigated the hydrolysis of the optically active L(-)-sec-butyl nitrate. This compound resembles the neutral sulfate and phosphate derivatives in that it is not an acid and yet it also resembles the alkyl hydrogen sulfates and alkyl dihydrogen phosphates since it only possess one organic radical. This point is important because the presence of two or three alkyl groups in an ester might be responsible for the impossibility of attack on the central atom (S, P or carboxylic C), whether as a result of steric hindrance or because of some special dielectric strength effect[3]. The study of sec-butyl nitrate will therefore permit us to decide with more certitude whether the conclusion made above, that retention of configuration and acid catalyzed hydrolysis are interrelated, is valid or not.

EXPERIMENTAL

Preparation of DL-sec-Butyl Nitrate

This compound was obtained by the procedure of Kornblum et al[4], by treating sec-butyl bromide or sec-butyl iodide with solid silver nitrate. Both methods were investigated and are described below. The use of sec-butyl bromide is preferable by far because the silver bromide formed during the reaction, unlike the silver iodide, forms a nice compact precipitate which does not absorb the liquid organic phase.

From sec-Butyl Iodide - 36.8 Grams (0.20 mole) of freshly redistilled sec-butyl iodide, were added slowly, from a dropping funnel, into a three-necked flask, fitted with sealed mechanical stirrer, a reflux condenser and containing 38.3 grams (0.225 mole) of very finely powdered silver nitrate. The vessel was kept in iced water and vigorous agitation was provided. After complete addition (one and one half hour,) the heterogeneous mixture, slowly turning to pale yellow, was stirred continuously for one hour while the temperature was allowed to rise slowly. The reflux condenser was then replaced by a short bent tube leading to a downward condenser, set for distillation. The receiving flask was cooled with dry ice and the distillation carried on under 50 to 70 mm pressure. Heating of the reaction flask (with a water bath) was continued until no more

liquid came over. 11.5 Grams of a slightly blue liquid were collected, shaken for one hour with 15 ml. of 85% phosphoric acid, washed three times with water, once with aqueous sodium bicarbonate, again two times with water and finally dried with anhydrous magnesium sulfate. Distillation at atmospheric pressure gave, without any trace of decomposition, a colorless liquid, boiling at 123.5°-124.0° and having a refractive index $n^{25}D$:1.4010; MD:(calculated): 28.80; found: 28.03; (Previous values[4,5]): b.p. 124°, $n^{20}D$: 1.4015. The yield was 10.8 grams or 45.6%.

From sec-Butyl Bromide - The same procedure was used throughout except for the fact that the silver bromide formed during the reaction came down as a compact solid, well separated from the liquid phase. This organic phase was tested for the absence of bromide ion, before distillation was started. The amounts employed were as follows: 13.7 grams (0.10 mole) of sec-butyl bromide, and 19.0 grams (0.112 mol) of silver nitrate; 10 gram of crude sec-butyl nitrate were recovered and shaken for 20 minutes with 10 ml. of 95% phosphoric acid. After washing, drying and redistillation, 8.3 grams (70%) of sec-butyl nitrate, b.p.:120°-125° $n^{25}D$: 1.4011, were obtained.

Preparation of L(-) sec-Butyl Nitrate

D(+)-sec-Butyl Iodide - The method of Clark[6], as used by Kornblum[4], was followed: 8.90 grams (0.12 mole) of L(-)-2-butanol[7], $[\alpha]^{25}D$ -13.05° (or approximately 96% optically pure), were added to 2.4 grams (0.0775 mole) of red phosphorus in a three-necked, 100-ml. flask, fitted with a reflux condenser, a thermometer and a sealed mechanical stirrer. 13.8 Grams (0.0545 mole) of iodine were slowly introduced through the third neck while the flask was being warmed slightly (35°) with an oil bath. After complete addition of the iodine (25 minutes), the reaction vessel was slowly heated for one and one half hour until the thermometer indicated 115°. After two hours standing at room temperature, the reflux condenser was replaced by a distilling head leading to a downward condenser and a receiver. Upon distillation, a mixture of 2-iodobutane and water came over. The organic phase was separated, washed with water, 10% aqueous sodium bicarbonate, water again and finally dried with anhydrous calcium chloride. Redistillation gave 11.5 grams of L(+)-sec-butyl iodide b.p.: 118-118.5°; $n^{25}D$; 1.5970; $[\alpha]^{25}D$ + 9.13°.

This result, (corresponding to + 9.59° if the starting material had been 100 per cent optically pure) is rather poor when compared with values found in the literature: (expressed as if derived from the optically pure alcohol):

$[\alpha]^{17}_{D}$ -31.98°[8]; using hydriodic acid at 0°; $[\alpha]^{21}_{D}$ + 40.7°[9], with phosphorus triiodide in carbon disulfide; $[\alpha]^{24}_{D}$ -18.70° [4] by this method.

The yield also is quite unsatisfactory (52% of the theoretical amount), but this may be due to the fact that the reaction was carried out as fast as possible in order to avoid extensive racemization.

D(+)-sec-Butyl Bromide - Several procedures are available for the preparation of this compound. Kenyon and his collaborators[10] have made an extensive investigation of the different methods and they indicate that their best result was obtained with phosphorus tribromide in ether solution: ($[\alpha]^{19}_{5461}$ + 8.02° from an alcohol $[\alpha]^{20}_{5461}$ - 7.09°). The yield however was very poor (29%).

Letsinger[11] obtained a compound with a much higher activity by passing dry hydrogen bromide into a mixture of 2-butanol and petroleum ether (30°-60°) at 5° C.; $[\alpha]^{25}_{D}$ -13.66° from an alcohol ($[\alpha]^{25}_{D}$ + 7.25° or $[\alpha]^{25}_{D}$ -26.1°, if one starts with an optically pure (+)-sec-butyl alcohol). His yield was 59 per cent.

After reading the various publications of Gerrard[12] on the replacement of hydroxyl group by halogen, we came to the conclusion that both Kenyon and his collaborators and Letsinger were working in the right direction and that the presence of an inert solvent, ethyl or petroleum ether for example, capable of dissolving hydrogen bromide, was absolutely desirable.

Procedure: To a solution of 7.4 grams (0.1 mole) of L(-)-2-butanol[7] ($[\alpha]^{25}_{D}$ -13.05) in 10-ml. of anhydrous ethyl ether in a 200-ml. three-necked flask, fitted with a sealed stirrer, a dropping funnel, a thermometer extending nearly to the bottom of the flask, and a reflux condenser, were slowly added 30 ml. (10.5 grams; 0.039 mole) of phosphorus tribromide (Eastman-Kodak, White Label). The vessel was cooled to -10° with an ice-salt mixture. The addition of the phosphorus tribromide took one and one-half hours, during which time stirring was continuously maintained and the temperature carefully kept below -10° C. When the addition was completed, stirring was continued for 5 hours while the reaction mixture was slowly allowed to come to room temperature. After 15 hours the reflux condenser was replaced by a distillation set-up, and after the ether was stripped out the 2-bromobutane was distilled under 60 mm. pressure and collected in an ice trap. The distillation was continued until no more liquid came over, even when the reaction vessel was heated to 100° and the pressure reduced to 25 mm. A syrupy residue was left in the flask, and this solidified on cooling.

The crude product (10 grams) was washed several times with water, 10% aqueous sodium carbonate, water again and finally dried with anhydrous magnesium sulfate. Fractional distillation through a 30-cm. helicoidal column gave 9.0 grams of pure D(+)-2-bromobutane, b.p.: 89.1-89.6°, n^{25}_{D}; 1.4347; $[\alpha]^{25}_{D}$ + 32.10° (α^{25}_{D} + 40.15°, pure liquid); yield, 66%. In another preparation, $[\alpha]^{25}_{D}$ + 32.21°, n^{25}_{D} :

1.4344, b.p. 89.2-.6°.

In conclusion, this modification of Kenyon's method seems quite successful. Since we started with a L(-) 2-butanol only 96% optically pure, the rotation of 2-bromobutane must be at least 33.43°. The yield could certainly be improved, especially if one considers that the loss of one gram during fractionation corresponds approximately to the hold up of the distillation apparatus.

C. L(-)-sec-Butyl Nitrate - The procedure followed was exactly the same as that described for the inactive material.

Using D(+)-sec-butyl iodide, $[\alpha]^{25}D$ + 9.13°, a nitrate was obtained with a rotation: $[\alpha]^{25}D$ -2.80° (pure liquid).

Using D(+)-sec-butyl bromide, $[\alpha]^{25}D$ + 32.21°, the product had the following properties: b.p.: 123-125°; $n^{25}D$: 1.40105, $n^{20}D$: 1.40165; $[\alpha]^{25}D$ -21.75°. The main batch of product, used in the following experiments, however, had a b.p.: 120.125°, $n^{25}D$; 1.4015, $[\alpha]^{25}D$ - 16.60° and must contain some unreacted bromide. No further purification was attempted. The yield could not be determined because of technical difficulties during fractionation.

Hydrogenolysis of L(-)-sec-Butyl Nitrate

Active sec-butyl nitrate, $[\alpha]^{25}D$ -4.15° (calcd.) was prepared by mixing 0.50-ml. of sec-butyl nitrate, ($[\alpha]^{25}D$ - 16.60°) and 1.50-ml. of the inactive material. This was dissolved in 5-ml. of anhydrous ether and slowly added to a

solution of 2.0 grams of lithium aluminum hydride in the same solvent, in a 50-ml. flask fitted with thermometer, dropping funnel and condenser. No reaction was visible at first although vigorous stirring was maintained all the time. After addition of approximately one half of the butyl nitrate, the reaction suddenly started and had to be carefully kept under control with a cold water bath. Addition was completed in one-half hour but the reaction continued for more than one hour. Heating was finally applied for thirty minutes after the spontaneous reaction had subsided. Then, with vigorous stirring and cooling in iced water, 2.0 ml. of water were very slowly added (2 to 4 drops per minute). A violent reaction takes place if these precautions are not observed and the mixture burns to ashes. Under proper conditions, the reaction slows down before all the water is added and the white precipitate which replaces the grey suspension of lithium aluminium hydride indicates that all the excess of reagent is decomposed. The mixture was then poured into 10-ml. of 10% aqueous sodium hydroxide and the aqueous phase separated and extracted four times with ethyl ether. The ether phase and the extracts were then joined together and summarily dried with anhydrous calcium sulfate. Upon distillation, the ether was removed and then 1.8 ml of an azeotropic mixture of 2-butanol and water (b.p. 86° to 98°) came over and, after thorough drying returned to the distilling flask. Finally,

0.855 gram of pure L(-)-2-butanol, b.p.: 98°-98.5° (748 mm) $[\alpha]^{25}_D$ - 7.68° (c = 7.75 weight per cent in DL-2-butanol) were recovered. This corresponds to an optical purity of 58.9%. The yield on a percentage basis is 66% assuming the nitrate to be approximately 95% pure.

Kinetics of Hydrolysis

The rate of hydrolysis was determined in 60 per cent aqueous dioxane (40% water by weight), in the presence of acid and base and under neutral conditions, by the usual acidimetric method.

The procedure was in all points the same as in the previous experiments and we refer to these for further details.

Stereochemistry of Hydrolysis

Here also the method was identical with that used in the experiments with L(-)-sec-butyl hydrogen sulfate. Method II, described in the experimental section, page 82 , was the only one employed for the measurement of the optical activity of the 2-butanol, at the end of the reaction.

RESULTS

The preparation of L(-)-sec-butyl nitrate was not particularly difficult. Since it was known that racemization occurs to a relatively large extent when an alkyl halide is treated with a silver salt, it was imperative to obtain a bromo or iodo-butane of high optical activity.

A slight modification of the method of Kenyon and collaborators[10], i.e., the use of phosphorus tribromide in ether solution at -10°, instead of room temperature, gave a product with a rotation $[\alpha]^{25}_{D}$ + 32.21°. Since one started with a product only 96% optically pure, the rotation of D(+)-2-bromobutane must be at least +33.43°. Kenyon's highest value was $[\alpha]^{14}_{5461}$ + 8.72°; although the dispersion coefficient is not given it is possible to calculate what the rotation would be for the sodium D line, by noting that the dispersion coefficient for sec-butyl bromide between other wavelengths is identical with that of sec-butyl alcohol. When this is done, one gets the approximate value $[\alpha]^{14}_{D}$ + 17.1° for the bromide, which is much lower than the one we observed. Letsinger's value[11] is also lower and, to our knowledge, 33.43° is the highest optical rotation ever indicated for 2-bromobutane.

The preparation of L(-)-sec-butyl nitrate from the bromide gave us a compound with $[\alpha]^{25}_{D}$ - 21.75°. The only available data on this active compound is given by Kornblum and coworkers[4] who obtained it as a by-product in the preparation of 2-nitrobutane; their product had a much lower

optical activity than ours: $[\alpha]^{25}_{D}$ + 7.02° (+ 8.25° if the starting material had been the optically pure alcohol).

The Configuration of (-)-sec-Butyl Nitrate

Although the reactions between an alkyl halide and a silver salt usually lead to inversion of configuration with extensive racemization, it was interesting to prove that the levorotatory sec-butyl nitrate had indeed the L configuration. In order to do this, the compound was reduced with lithium aluminum hydride in anhydrous ether. 2-Butanol was recovered from the reaction mixture in 66 per cent yield and with a rotation: $[\alpha]^{25}_{D}$ -7.68°.* Since it is reasonably certain that the reduction proceeds without affecting the alkyl-oxygen bond, one can safely assume that the configuration is retained. The alcohol recovered had only 58.9 per cent of its original activity; racemization has therefore occured during bromination and nitration to the total extent of 41.1 per cent.

The Hydrolysis of L(-)-sec-Butyl Nitrate

Kinetics

The rate of hydrolysis of sec-butyl nitrate was measured at 75° and 81° in 60 per cent aqueous dioxane. This solvent mixture was chosen, partly because of the insolubility of the ester in water and partly because it was the one most convenient for the stereochemical investigation coming later.

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* Since (-)-2-butanol has the L- configuration, (-)-2-butyl nitrate must also be L.

The kinetics in acidic and neutral conditions were perfectly first order and the rate constants in both of these media are practically identical, showing the absence of acid catalysis (Table 2).

Under basic conditions, difficulties were encountered because of the extreme slowness of the hydrolysis as compared with the reaction of the alkali with the pyrex glass of the ampoules. The use of stainless steel vessel with lead gasket was tried but over the long period of time required for the reaction to proceed, evaporation was not negligible and the results were not any better. Out of four determinations, only one was fairly reliable and indicated that the reaction is base catalyzed.

The results are summarized in Table 2:

Table 2

HYDROLYSIS OF sec-BUTYL NITRATE

Solvent: 60% aqueous dioxane

Temperature	Ester M	$HClO_4$ M	NaOH M	$k_1 \times 10^6$ sec^{-1}
81	0.08403	----	----	4.22
81	0.08403	0.08470	----	4.10
76	0.08401	----	0.1201	7.71

Stereochemistry

The method used to determine whether or not a Walden inversion takes place during the hydrolysis of L(-)-sec-butyl nitrate, was exactly the same as that used in the similar experiments on L(-)-sec-butyl hydrogen sulfate. In order to have a sufficiently high concentration of 2-butanol at the end of the hydrolysis, it was necessary to use higher concentration than in the kinetic experiments. The solubility of the ester in 60 per cent aqueous dioxane is rather low however, and it was necessary to work with heterogenoeus mixtures which slowly became homogeneous as the reaction progressed.

1.025 grams of optically active nitrate, $[\alpha]^{25}D$ - 16.60°, and 0.031 grams of the inactive ester were hydrolyzed in 50-ml. of 60 per cent aqueous dioxane at 50°, in a sealed 100-ml. ampoule. The solution became homogeneous within less than four days. After five days, the hydrolysis had progressed to the extent of 5 per cent as shown by an acid titration. The ampoule was then placed in a bath at 75° and after 15 days and 19 hours, 30 per cent of the theoretical amount of acid was formed; this corresponds to a specific rate constant of approximately 3.5×10^{-6} sec.$^{-1}$, a value which is quite reasonable in view of the previous kinetic experiments (Table 2).

Since racemization of the alcohol can be rather extensive under these conditions,[13] the solution was neutralized

at this point and the organic phase salted out with potassium carbonate, dried in stage with the same reagent and slowly distilled. Five fractions were collected between 85 and 100°, two of them were analyzed; they are indicated in Table 3 with their rotation and their refractive indices. The values for the absolute rotations were determined by the method used before; this is based on the relation between the refractive index and the concentration of a solution of 2-butanol in anhydrous dioxane. It is noted that the alcohol is D, whereas the nitrate was L; thus there has been inversion during the hydrolysis.

Table 3

PROPERTIES OF sec-BUTYL ALCOHOL RECOVERED FROM ACID HYDROLYSIS OF sec-BUTYL NITRATE IN 60% AQUEOUS DIOXANE

Fraction b.p.:	$\alpha^{25}D$	$n^{25}D$	% butanol	$[\alpha]^{25}D$
96.8-98.5	+0.090	1.4165	7.4	+1.23 ± 0.12
98.5-100	+0.055	1.4180	3.3	+1.72 ± 0.35

Although these values are not very accurate, they nevertheless demonstrate sufficiently well that inversion of configuration has indeed occurred during hydrolysis. An average value for the specific rotation, giving the first measurement, twice the weight of the second, since it is more accurate is $[\alpha]^{25}D$ + 1.35°. Since the nitrate was only one half of 59 per cent optically pure, or 29.5 per cent, the extent of

optical inversion is 35% as given by the following relationship:

$$\frac{1.35}{13.05 \times 0.295} = 35\%$$

DISCUSSION AND CONCLUSIONS

The rate of hydrolysis of tert-butyl nitrate was measured by G. R. Lucas and L. P. Hammett[14]. In 60-per cent aqueous dioxane, in the absence of either base or acid, the specific rate constant at 25° was found to be 1.653×10^{-3} sec^{-1} for an initial ester concentration of 0.05111 mole per liter. Using these authors' value for the activation energy in this particular solvent, 22,870 cal/mole, one can calculate the specific rate constant at 81° : 0.736 sec^{-1} or 1.74×10^{5} times faster than that of sec-butyl nitrate. The corresponsing values for tertiary and secondary butyl chlorides, in 50 per cent ethanol (by volume) at 90°[15,16] are 0.358 and 1.50×10^{-5} or a ratio of 2.39×10^{4}. Comparison of these two ratios indicates a remarkable similarity between the two systems. The difference of solvents is probably responsible for the smaller value in the case of the chloro derivatives. It is possible therefore that, like the secondary halides, sec-butyl nitrate is hydrolyzed by a combination of uni- and bimolecular mechanisms (S_N1 and S_N2). This view is substantiated by the observation that the hydrolysis of the secondary nitrate is catalyzed by hydroxyl ions, while that of the tertiary derivative is not[14].

As to whether or not the hydrolytic reaction involves a displacement on the nitrogen atom, all the evidence indicates that no such mechanism has occured. The alcohol

recovered after hydrolysis showed an inverted configuration and the extensive loss of activity was largely due to its independent racemization under acid conditions. (Refer to pages 86, 95, for a measure of the rate of racemization of L(-)-2-butanol under acid conditions).

It appears therefore that the observation made before that hydrolyses , not subject to acid catalysis, take place with inversion of configuration is also valid in the case of the alkyl nitrates. It is probable that a water molecule is not capable by itself of attacking the central atom of an "oxygenated" group, such as sulfate, phosphate, nitrate, carboxylate or others. When however the negative charge on one of the oxygen atoms, whether formal or not, is neutralized by a proton or when the oxygen is replaced by a halogen atom, then a displacement on the central atom becomes possible and retention of configuration occurs.

Similar requirements exist for basic hydrolysis, the only difference being that formal charges are no longer obstacles for the powerful nucleophilic hydroxyl ions. If however the "oxygenated" group bears a negative charge, as in the case of the monoalkyl sulfates, then hydrolysis proceeds by an entirely different mechanism, viz., a nucleophilic displacement on the alkyl carbon atom, and retention of configuration is not possible.

We were not able to determine whether or not a Walden inversion accompanies the basic hydrolysis of L(-)-sec-butyl nitrate. As soon as some potassium hydroxide was added to

a solution of the ester in 50 per cent aqueous dioxane, two phases separated and not much change was observed even after standing two weeks at 80°. Solution was only possible at very low concentrations where the error of measuring optical activity would have been so large that the results would be without significance. The use of a strong organic base in the same or different solvent might be more successful and is certainly worthwhile investigating.

In conclusion, we believe that one can regard the esters of inorganic acids as being hydrolyzed by a combination of the mechanisms usually postulated for the hydrolysis of alkyl halides on one hand and of primary and secondary carboxylic esters on the other. Depending on the conditions, such as the nature of the ester, the possibility of acid catalysis (which depends on the basicity of the ester) and the pH, nucleophilic character and solvation power of the solvent, one of the three mechanisms (S_N1, S_N2 or S_Ni) predominates and the result is, as we have seen, racemization, inversion or retention of configuration. The observations summarized in Table 1, page 131, indicate further that some carboxylic esters, usually derived from tertiary alcohols, also show some ability to react by the three mechanisms and one can safely say that if no alkyl halides show any tendency to undergo hydrolysis with "frontal" rearrangement (S_Ni), it is only because no such rearrangement is possible.

There is no need therefore to differentiate sharply between the hydrolysis of an alkyl halide and that of a

carboxylic ester and, in fact, the three mechanisms listed above are probably the consequences of the adjustment of each ester molecule to its surroundings, so that it can undergo the process of hydrolysis with the least possible expenditure of energy.

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APPENDIX

THE PREPARATION OF L(-)-2-BUTANOL FROM D(-)-2,3-BUTANEDIOL

by

P. J. Leroux and H. J. Lucas[1]

L(-)-2-Butanol from D(-)-2,3-Butanediol[1]

The ready availability of D(-)-2,3-butanediol, Fig. 1, through fermentation methods[2] and the satisfactory yields realized in former work with active and inactive compounds[3,4] has led to the preparation of L(-)-2-butanol, ninety nine per cent optically pure, from the active glycol in forty nine per cent yield through the steps: D(-)-2,3-butanediol, I, D(+)-2,3-diacetoxybutane[4], II, L(+)-erythro-3-chloro-2-butanol[3,4], III, D(+)-2,3-epoxybutane[3], IV, and L(-)-2-butanol, V (Fig. 1). The last step, the reduction of the oxide to the alcohol, has been accomplished with lithium aluminum hydride, following the procedure of W. G. Brown and co-workers[5]. As solvent absolute ethyl ether gave the best results; the yield was eighty per cent. Tetrahydrofuran is less satisfactory, largely because separation by distillation is more difficult. Reduction of L(+)-erythro-3-chloro-2-butanol was attempted but the yield was low with either tetrahydrofuran or ethyl ether as solvent.

The conversion of D(+)-2,3-epoxybutane to L(-)-2-butanol is a confirmation of the configuration of the oxide[3]. The overall conversion from D(-)-2,3-butanediol requires more steps than were involved in the original determination of the glycol configuration by Morell and Auernheimer[6], but the high temperature required in the decomposition of the glycol diacetate caused some racemization. Moreover the intermediate methyl vinyl carbinol that they reduced to

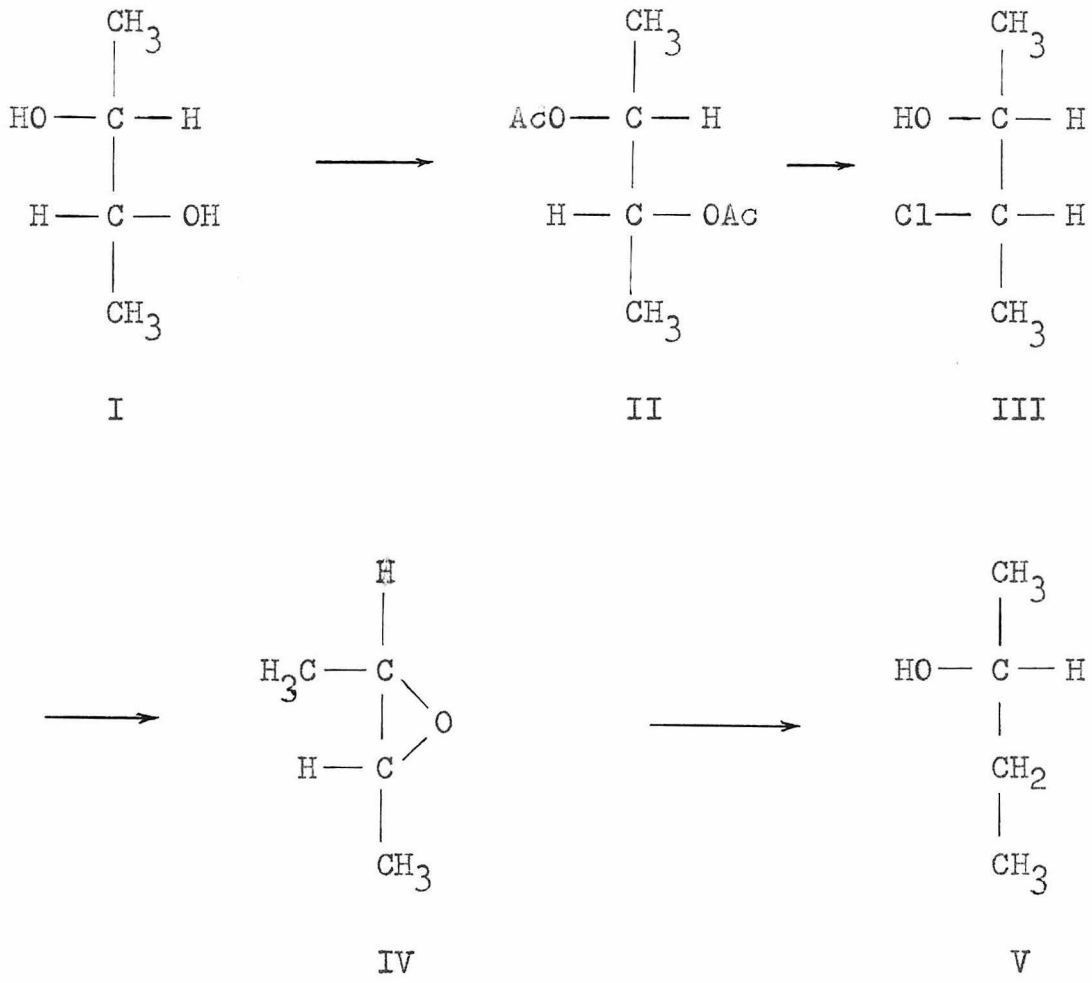

Fig. 1 CONVERSION OF D(-)2,3-BUTANEDIOL TO L(-)-2-BUTANOL

2-butanol was a byproduct, not the main reaction product.

An overall yield of 45 to 48% would be expected by way of the oxide, in view of the yield at the last step and previous results, some with active compounds[3], others with inactive compounds[4]. By raising the yield of chlorohydrin from 70 to 77 per cent, an overall yield of forty nine per cent has been obtained. The yield at the last step probably can be increased to ninety per cent, to bring the overall yield to over fifty per cent.

The active alcohol has $\underline{d}^{25}4$ 0.8042, $\underline{n}^{20}\underline{D}$ 1.3970, $\underline{n}^{25}\underline{D}$ 1.3949, $a^{25}\underline{D}$ -10.67°, $[\alpha]^{25}\underline{D}$ -13.51°. This compares with $\underline{d}^{27}4$ 0.8025 ($\underline{d}^{25}4$ 0.8041, interpolated), $\underline{n}^{20}\underline{D}$ 1.3954, $[\alpha]^{27}\underline{D}$ +13.52($[\alpha]^{25}\underline{D}$ +13.63°, interpolated) for the purest dextro alcohol described[7]. If the active alcohol of Pickard and Kenyon is taken as one hundred per cent, the product from 2,3-butanediol has about one per cent impurity (including any DL-alcohol), calculated from the specific rotation. The density of our alcohol checks that of theirs, but the refractive index is not in good agreement[7].

The advantages of the method are convenience, reasonably good yield and high optical purity. The preparations are easy and with the exception of 3-chloro-2-butanol can be carried out with reasonable rapidity. Although the chlorohydrin requires a standing time of two to three weeks, the actual preparation is not laborious. The standard method of resolution of the acid phthalate of 2-butanol with brucine[9] gives about a forty per cent yield of (+)-alcohol after five to seven crystallizations, $[\alpha]^{27}\underline{D}$ + 10.83°.

Thus although the precentage yields are comparable, the new method is less laborious and gives a much purer product.

EXPERIMENTAL

D(+)-2,3-Diacetoxybutane, II. - The glycol[10], I, was distilled at 10 mm. b.p. 77.5-78°, α^{25}_{D} -12.92°, $[\alpha]^{25}_{D}$ [11] -13.09°. To 180 grams (2 moles) of I was added 450 grams (4.4 moles) of freshly distilled acetic anhydride and 800 grams freshly distilled pyridine. After standing over night volatile impurities were removed by distillation at 10 mm., followed by II; b.p. 82°, α^{25}_{D} + 13.87°, slightly lower than + 14.10 of recrystallized product[3], yield 319 grams, 91.5%.

L(+)-erythro-3-Chloro-2-butanol, III. - Gaseous hydrogen chloride was passed into a solution of 315 grams (1.81 mole) of II in 460 grams concentrated hydrochloric acid at -18° to -20° in two 1-liter ampoules until 162 grams was absorbed. The ampoules were sealed and the solutions allowed to stand at room temperature for three weeks. The solutions were poured over one kilo of powdered technical sodium bicarbonate, the inorganic solids were removed by suction filtration, the organic liquid was separated, the salt cake was washed with isopropyl ether and the aqueous phase was extracted with isopropyl ether. Following washing of the combined organic phase with aqueous sodium bicarbonate, it was filtered through dry ice to remove water. Distillation gave 150 grams of crude III (yield, 76.5%, overall, 70%), p.p. (10 mm.) 56-62°, $[\alpha]^{25}_{D}$ +9.77. The boiling range and

high rotation[12] can be ascribed to the presence of some chlorohydrine acetate, but this is no particular detriment because it is converted into IV at the next step.

D(+)-2,3-Epoxybutane, IV - Into a 125-ml. flask containing a solution of 250 grams of potassium hydroxide pellets in 125 ml. of water maintained at 90° to 95° was slowly added 37.6 grams (0.348 mole) of III, IV distilling as formed. Finally the temperature was raised to boiling, to drive over all oxide. After drying the two-phase distillate (without separation) with potassium hydroxide, 22 grams of IV distilled at 53.5 at 746 mm., α^{25}_{D} +46.75°, slightly lower than previous value[3] of +47.23°; yield 88%, overall, 61.6%.

L(-)-2-Butanol, V - To a solution of 5 grams (0.132 mole) of lithium aluminum hydride (Metal Hydride Inc.)[13] in 150 ml. absolute ether, 22 grams (0.306 mole) of IV was added slowly with stirring over a period of one hour, at a rate to produce gentle boiling of the solvent. Refluxing was continued for another hour. Following addition of 20 ml. water during cooling, the mixture was poured into 50 ml. of 10% aqueous potassium hydroxide and the aqueous phase was extracted four times with ethyl ether. After drying with anhydrous potassium carbonate, fractional distillation gave 18.1 grams of V, b.p. (745 mm.) 97.5-98.0°, α^{25}_{D} -10.67°, $[\alpha]^{25}_{D}$ -13.51°; yield, 80%, overall, 49.3%.

SUMMARY

The reduction of D(+)-2,3-epoxybutane to L(-)-2-butanol with lithium aluminum hydride proceeds smoothly and gives a good yield of active alcohol having an optical purity of ninety nine per cent. The overall yield of alcohol from D(-)-2,3-butanediol is about fifty per cent.

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8. We obtain for redistilled DL-2-Butanol, also dried with potassium carbonate, $n^{20}D$ 1.3969, $n^{25}D$ 1.3949, in good agreement with our values for the active alcohol, and with $n^{25}D$ 1.39495, obtained with thoroughly dried DL-a-butanol, b.p. (760 mm.) 99.259°; R. Brunel, This Journal, 45, 1337 (1923).

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10. We are indebted to Dr. G. A. Ladingham, Director, and to Drs. A. C. Neish and J. A. Wheat of the Division of Applied Biology, National Research Council of Canada, for a supply of the active glycol, obtained by fermentation of starch with Aerobacillus polymyxa. We take this occasion to express our appreciation of this courtesy.

11. Previous values,[2,6] -13.0°, -13.19° and -13.34°; also -12.85°.

12. Previous value[3] for L(+)-erythro -3-chloro-2-butanol, $\alpha^{25}D$ + 9.47°.

13. An excess was taken to insure a sufficient amount, because the container had been opened a number of times, with possible deterioration of the reagent.

PROPOSITIONS

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Proposition No. 1.

In most of the solvolytic reactions of optically active compounds for which a carbonium ion has been postulated, significant inversion of configuration is almost generally observed[1,2]. This may be interpreted as indicating that solvation of the carbonium ion does not occur on both sides of the asymmetric carbon atom with equal ease.

Probably the most logical explanation of this effect is that ionization of the original dipolar compound and solvation of the newly formed carbonium ion are almost simultaneous[3]. In other words, it is very doubtful that a "free" carbonium ion exists in solution at any time, except possibly in the case of the triphenylcarbinyl derivatives and similar compounds.

Hughes and Ingold[4], in their theory of the unimolecular (S_N1) solvolysis of alkyl halides, claim that a decrease of the solvation power of the medium should produce an increase in the extent of racemization, since the lack of reactivity of the medium allows enough time for the carbonium ion to assume its planar configuration, before substitution intervenes.

We believe that their way of reasoning is wrong in this case since, on the basis of what is indicated above, the fate of the carbonium ion, i.e. its future configuration, is determined during the process of ionization and not after.

We propose therefore to show that a result exactly opposite to that predicted by Hughes and Ingold should be observed and we shall present some experimental evidence taken from the literature[5] in favor of our proposition.

Proposition No. 2.

In 1948, Grunwald and Winstein[6] proposed a scheme for the correlation of the solvolysis rates, based on the ractivity of tert-butyl chloride, an ester which is known to undergo normally unimolecular solvolysis.

Instead of basing their treatment onaphysical constant such as the dielectric strength, these authors preferred to compare the rate of solvolysis of a given ester in different solvents, with that of tert-butyl chloride in the same set of solvents. Although a fair correlation between the rates of unimolecular solvolysis of a series of esters was obtained that way, limitations were immediately encountered.

We propose to show how Grunwald and Winstein's empirical treatment could be profitably related to the theories of Laidler and Eyring[7,8] and others on the interaction between dipolar molecules in solution. From this we shall explain the nature of the limitations encountered by Grunwald and Winstein.

Proposition No. 3.

Further evidence in favor of the postulated mechanisms of solvolysis of alkyl hydrogen sulfates[9] and phosphates[10] could easily be obtained from a study of the hydrolysis under acidic, neutral and basic conditions of the following esters: α-methyl-allyl hydrogen sulfate, crotyl hydrogen sulfate and eventually the corresponding dihydrogen phosphates.

Proposition No. 4.

Threo-3-Chloro-2-butanol has not been obtained optically active. We propose a method for its preparation, starting from L(+)-erythro-3-chloro-2-butanol, easily available[11], and involving three steps, namely: tosylation, acetylation and hydrogenolysis.

Proposition No. 5.

The esters of sulfuric acid are in general much easier to handle than the corresponding phosphates. Since the reactions of both types of compounds are fairly similar, especially their hydrolysis, it would be interesting to study more extensively the comportment of acid and neutral sulfates of diols as this would probably help in clarifying the mechanism of exchange of phosphate residues between different hydroxyl groups in the metabolism and in the enzymatic degradation of carbohydrates.

Proposition No. 6.

The possibility of a correlation between the oxydo-reduction potentials of the systems quinone-hydroquinone and the resonance energy of these molecules has been investigated quite extensively[12]. We propose to show that a similar treatment could be applied to the systems ketone-tert-alcohols for which oxydo-reduction potentials have been determined[13].

Proposition No. 7.

When the bread mold Neurospora is used in biochemical investigations, the presence of a mutation affecting some essential part of the organism is detected by the absence of

normal growth on minimal medium. This is unfortunately the only criterion available and we are led to think that in some cases, the experimenter might be misled by the presence of unsuspected mutations, affecting some non-essential step but capable of influencing the vital mechanism, under some specified conditions. The existence of temperature mutants could possibly be explained on such a basis(14).

Proposition No. 8.

The mutant strain of Neurospora # 80702 is known to be blocked at the thiosulfate level in the biochemical synthesis of cysteine. After working for some time with that mutant, mainly trying to isolate an oxidation product of cystine or cysteine which would successfully replace thiosulfate, we came to the conclusion that at least one oxidation product of cystine is biologically active and that it is probably cystine disulfone. This compound however could not be obtained in a pure form and the problem remained more or less unsolved. We believe that some further work should be continued on this line and we suggest that aliphatic disulfones and disulfoxides and other compounds of the type $R\text{-}SSO_3Na$ be tested for biological activity(15).

Proposition No. 9.

The recent work of Hubbard and Luder(16) on the catalytic action of aluminum chloride, ferric chloride and stannic chloride in the reaction of metals with thionyl chloride suggest that these catalysts be tried in the reactions of thionyl chloride, phosphorus trichloride and phosphorus pentachloride with alcohols. A positive result would favor the mechanism put forward by Gerrard(17) for these last reactions.

Proposition No. 10.

The use of "polyethylene" bottles might prove advantageous for running reaction kinetics at temperatures up to at least 50° in the presence of alkali. Until now, one had to use stainless steel vessels which are expensive and often are not sufficiently air-tight.

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